# Steps Towards Personalised Antibiograms

*predicting antimicrobial susceptibility*

Sanden, Line Rugholm

*DOI (link to publication from Publisher):*
10.5278/vbn.phd.med.00095

*Publication date:*
2017

*Document Version*
Publisher's PDF, also known as Version of record

# STEPS TOWARDS PERSONALISED ANTIBIOGRAMS

PREDICTING ANTIMICROBIAL SUSCEPTIBILITY

**BY**
**LINE RUGHOLM SANDEN**

DISSERTATION SUBMITTED 2017

AALBORG UNIVERSITY
DENMARK

# STEPS TOWARDS PERSONALISED ANTIBIOGRAMS

## PREDICTING ANTIMICROBIAL SUSCEPTIBILITY

by

Line Rugholm Sanden

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2017

.

Dissertation submitted: March 2017

PhD supervisor: Prof. Steen Andreassen,
Aalborg University

PhD committee: Professor Svend Birkelund
Aalborg University

Emeritus Professor Ewart Robert Carson
City University London

Ledende overlæge, professor dr. med.
Vejle Sygehus

PhD Series: Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-935-9

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk



Printed in Denmark by Rosendahls, 2017

# CV

**Personal Information**

Line Rugholm Sanden
Born September 17, 1984, Aalborg, Denmark

**Academic Profile and Research Experience**

Line received her Master of Science (MSc) in Biomedical Engineering and Informatics from Aalborg University, Denmark in 2009. Line began her PhD studies at Aalborg University's Department of Health Science and Technology in 2009. During the PhD study, she had contributions accepted at two international conferences, two papers published and submitted a patent application.

**Current and Prior Positions**

Research Assistant, Centre for Health Informatics, University of New South Wales, Sydney, Australia, 2008

PhD Student, Center for Model-Based Medical Decision Support, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark,
November 2009 – March 2017

Quality Assurance Manager, Treat Systems Aps, Aalborg Denmark,
September 2014 - Present

# ENGLISH SUMMARY

Antimicrobial treatment of infectious patients is increasingly complicated by frightening rates of antimicrobial resistance in infection-causing pathogens. The development of antimicrobial resistance is driven by the use and misuse of antimicrobials. Therefore, the choice of antimicrobial treatment should be appropriate to achieve the best outcome for both current and future patients. Hospitalised patients suspected of infection are often treated empirically with antimicrobials (i.e. before microbiological results on pathogen identity and antimicrobial susceptibility are available). Institutional antibiograms (ABG), which are aggregated local antimicrobial susceptibility test (AST) results, can be used as an indicator for the expected susceptibility to antimicrobials, when choosing empirical antimicrobial treatment.

The aim of this project was to generate personalised ABGs, which predict patient-specific antimicrobial susceptibility in the hospital setting. During the project, we focused on making the results of the research operational, by developing practical implementable applications. This thesis summarises the research and methods developed to generate personalised ABGs as a series of steps taken, starting with the institutional ABG.

The first step was to generate ABGs representing patients with hospital-acquired infections and patients with community-acquired infections, respectively. Typically, AST results are available for a limited set of antimicrobials. When patient-specific AST results become available, and a treatment must be chosen, cross-resistance and cross-susceptibility for all available treatments must be considered. The next step was therefore to develop and validate a method which uses cross-susceptibility/resistance to adjust an ABG with respect to a patient's AST results (Paper I). The next patient-specific factor considered was the association between prior antimicrobial exposure and increased resistance at the patient level (Paper II). The results indicate to which degree the susceptibilities should be adjusted, for patients previously exposed to antimicrobials. A mathematical method was developed to modify the ABG with respect to a patient's prior antimicrobial exposure. This method also served as an operationalisation of Paper II. The method was extended to modify the ABG with respect to both patient-specific prior exposure to antimicrobials and AST results (Patent pending). Future work involves the validation of this method. During the project the developed methods were implemented in an existing software solution for antimicrobial stewardship, Treat Steward.

# DANSK RESUME

Antimikrobiel behandling af infektioner er i stigende grad kompliceret af øget resistens hos de patogener, som forårsager infektioner. Udvikling af antimikrobiel resistens er drevet af brugen og misbrugen af antimikrobielle stoffer. Derfor bør valget af antimikrobiel behandling været særdeles velovervejet for at opnå det bedste resultat for både nuværende og fremtidige patienter. Indlagte patienter med tegn på infektion behandles oftest empirisk med antimikrobielle stoffer, før der forelægger mikrobiologiske resultater om patogen-identitet og antimikrobiel resistens. Institutionelle antibiogrammer (ABG), som er aggregerede lokale suceptibilitets-resultater, kan bruges som en indikator for den forventede susceptibilitet, når der vælges empirisk antimikrobiel behandling.

Formålet med dette projekt var at skabe patientspecifikke ABG'er, der prædikterer antimikrobiel susceptibilitet hos indlagte patienter. I løbet af projektet, var der fokus på at gøre forskningsresultaterne operationelle, ved at udvikle praktiske implementerbare metoder. Denne afhandling opsummerer forskningen og metoderne udviklet til at generere patientspecifikke ABG'er.

Det første skridt var at generere ABG'er til at repræsentere henholdsvis patienter med hospitalserhvervede infektioner og patienter med samfundserhvervede infektioner. AST resultater bliver typisk kun tilgængelige for et begrænset sæt af antimikrobielle stoffer. Når patientspecifikke AST resultater bliver tilgængelige, og skal vælges en behandling, bør kryds-susceptibilitet/resistens til alle tilgængelige behandlinger tages i betragtning. Det næste trin var derfor at udvikle og validere en metode, som anvender kryds-susceptibilitet/resistens til at justere et ABG i forhold til en patients AST resultater (Paper I). Den næste patient-specifikke faktor, der blev taget i betragtning var sammenhængen mellem tidligere antimikrobiel behandling og øget resistens på patientniveau (Paper II). Resultaterne indikerer i hvilket omfang susceptibiliteten skal justeres for patienter, som tidligere har modtaget antimikrobiel behandling. En matematisk metode blev udviklet til at modificere ABG'et i forhold til en patients tidligere antimikrobielle behandling. Denne metode fungerede også som en operationalisering af Paper II. Metoden blev udvidet til at justere ABG'et med hensyn til både en patientens tidligere behandling med antimikrobielle stoffer og patientens AST resultater (patentanmeldt). Det fremtidige arbejde involverer valideringen af denne metode. I projektet blev de udviklede metoder implementeret i TREAT Steward, som er en eksisterende softwareløsning til "antimicrobial stewardship".

# PREFACE

This PhD thesis includes both published and unpublished material. Chapter 2 includes an abstract accepted for presentation at the 27th European Congress of Clinical Microbiology and Infectious Diseases (Vienna, April 2017). Material in the form of two published papers forms the basis of Chapter 3 and Chapter 4, respectively. Additionally, the thesis includes a mathematical method which is described in a patent application. The chapters based on published material are written as extended summaries, while those which present unpublished material are written in the form of chapters in a monograph.

The work was carried out at the Center for Model-based Medical Decision Support, Department of Health Science and Technology at Aalborg University in Denmark. The PhD project contributes to the existing project of developing the decision support system for antimicrobial stewardship; Treat Steward, which had its origin in the same department.

During the project, my focus has been on making the research operational, by developing practical applications, with the aim of shortening the way from research to an implemented solution available for clinicians and patients.

# ACKNOWLEDGEMENTS

There are a number of people without whom this thesis might not have been written.

First, I would like to thank my PhD supervisor Prof. Steen Andreassen for his invaluable comments and original ideas. I would also like to thank Prof. Mical Paul and Prof. Leonard Leibovici for their insights as co-authors, for provision of data, and suggestions throughout my project.

I would also like to thank my friends and colleagues at MMDS, Judex, amPHI Systems, and TREAT Systems. A special thanks goes to Ulrike Pielmeier and Mads Mogensen their understanding, encouragement and moral support. Also, thanks to Logan Ward for minimising the "danglish".

Thank you to my family and friends who have supported me along the way. Thanks to Marianne Bystrup for showing up in the most stressful periods and being so supportive and enthusiastic in all matters.

Last but certainly not least, a very special thanks to my husband Esben for not letting me give up and for the never ending practical and emotional support, especially as both our children were born during the project period.

# TABLE OF CONTENTS

**Chapter 1. Introduction** ..... **17**

**Chapter 2. Institutional ABGs** ..... **22**

2.1. Quality-check of the isolate database ..... 23

2.2. Mapping species into pathogen groups ..... 25

2.3. Hospital and community ABGs ..... 30

2.4. Filling in the gaps in the ABGs ..... 33

2.5. Including cross-susceptibility/resistance in the ABG ..... 37

**Chapter 3. Interpretative reading of AST results** ..... **41**

3.1. Introduction ..... 42

3.2. Calculating posterior susceptibilities ..... 42

3.3. Validation of the explored methods ..... 46

3.4. Discussion and conclusion ..... 50

**Chapter 4. The effect of prior antimicrobial exposure** ..... **51**

4.1. Introduction and Method ..... 51

4.2. Resistance in GN bacteria to single antimicrobials ..... 52

4.3. Resistance in GP bacteria to single antimicrobials ..... 54

4.4. Resistance in GN bacteria to classes of antimicrobials ..... 55

4.5. Discussion and conclusion ..... 56

**Chapter 5. Modifying the ABG to account for PE** ..... **58**

5.1. The susceptibility to an antimicrobial after PE to the same antimicrobial class ..... 58

5.2. The susceptibility to an antimicrobial after PE to other classes of antimicrobials ..... 61

**Chapter 6. Modifying the ABG to account for both PE and AST** ..... **64**

**Chapter 7. Implementing the personalised ABG** ..... **68**

7.1. TREAT Steward ..... 68

7.2. Implemetation in TREAT Steward ..... 70

7.3. Patient example ..... 71

**Chapter 8. Discussion** ..... **75**

**Literature list**.....**77**
**Appendices**.....**81**

# LIST OF PUBLICATIONS

This thesis includes the following publications. The papers are referenced in the text by their corresponding roman numerals.

**Paper I:** Andreassen, S., Zalounina, A., Paul, M., Sanden, L., Leibovici, L., 2015. Interpretative reading of the antibiogram – a semi-naïve Bayesian approach. Artif. Intell. Med. 65, 209–217

**Paper II:** Sanden, L., Paul, M., Leibovici, L., Andreassen, S., 2016. Quantifying the associations between antibiotic exposure and resistance - a step towards personalised antibiograms. Eur. J. Clin. Microbiol. Infect. Dis. 35, 1989–1996

**Conference abstract:** Sanden, L., Hussein, H., Paul, M., Andreassen, S., 2017. Pathogen- and antimicrobial-specific resistance in late hospital-acquired infections. In: The 27th European Congress of Clinical Microbiology and Infectious Diseases. (Accepted)

# LIST OF ABBREVATIONS

| | |
|---|---|
| ABG | Antibiogram |
| AmoCl | Amocixillin-Clavulanate |
| Ampi | Ampicillin |
| AST | Antimicrobial Susceptibility Test |
| CAI | Community-Acquired Infection |
| Cftax | Ceftriaxone |
| EUCAST | The European Committee on Antimicrobial Susceptibility Testing |
| GN | Gram Negative |
| GP | Gram Positive |
| HAI | Hospital-Acquired Infection |
| InstABG | Institutional Antibiogram |
| NOSO | Nosocomiality |
| OD | Odds |
| OR | Odds Ratio |
| PE | Prior Exposure |
| PipTa | Piperacillin-Tazobactam |

# CHAPTER 1. INTRODUCTION

*This chapter gives an introduction to the challenges that motivate this project, followed by an introduction to the scope of the project, describing the clinical area to which the project contributes. Finally, the research objectives addressed in each chapter are presented.*

Antimicrobial resistance is recognised by the WHO (World Health Organisation) as a major health threat of the 21st century. Resistance to the currently available antimicrobials currently claim upwards of 50,000 lives each year across Europe and the US (WHO, 2014).

---

*"Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill."*

Dr Keiji Fukuda **(**WHO Assistant Director-General for Health Security)

---

The emergence and spread of antimicrobial resistance is driven by the continued use and misuse of antimicrobials. The majority of human consumption of antimicrobials occurs in the community (outside hospitals). Nevertheless, antimicrobial consumption in hospitals is a main driver for the spread of antimicrobial-resistant bacteria responsible for healthcare-associated infections (ECDC, 2015). This thesis focuses on the use of antimicrobials in the hospital setting. It is in the hospital setting that the most extreme drug resistance has been found and the broadest-spectrum antimicrobials are being used (Doron and Davidson, 2011). The selection of resistant bacterial strains in individual hospitalised patients that is caused by antimicrobial exposure also have potential ecological implications in the community, through the spread of resistant strains (Timothy H. Dellit et al., 2007). Unfortunately, the extensive use of antimicrobials continues to increase; as an example the latest data on the overall antimicrobial consumption in the EU hospital sector (2010–2014) showed a significant increasing trend (ECDC, 2015). Moreover, an estimated 20-50% of all antimicrobials prescribed in the hospital setting are either unnecessary or inappropriate (CDC, 2016; Timothy H. Dellit et al., 2007; Doron and Davidson, 2011).

The threat of resistance can be effectively mitigated either by the discovery of new antimicrobials or by a more appropriate use of antimicrobials. The already small and dwindling pipeline of drug candidates makes it unlikely that the rescue will come

from newly discovered drugs (WHO, 2014, 2011). The course of action, most likely to succeed, is to find ways of using the existing antimicrobials more prudently.

Actions have been taken worldwide, where hospital based antimicrobial stewardship Programmes have been incorporated into hospital policies. The term antimicrobial stewardship covers coordinated interventions, to improve the quality of antimicrobial use. The primary goal is to optimise clinical outcomes and ensure cost-effectiveness of therapy, while minimizing unintended consequences of antimicrobial use, including toxic effects, selection of pathogenic organisms, and the emergence of antimicrobial resistance (CDC, 2016; Timothy H Dellit et al., 2007).

The use of IT-based interventions, including decision support systems, have been shown to improve the appropriateness of antimicrobial prescribing in hospitals and present an exciting new prospect to target inappropriate antimicrobial prescribing (Baysari et al., 2016; Kullar et al., 2013; MacDougall and Polk, 2005).

When a patient presents at a hospital and is suspected of having an infection, antimicrobials will be administered to the patient with the purpose of eradicating the microorganism causing the infection. Choosing an appropriate antimicrobial treatment is a complicated task where a number of factors must be considered. First, the clinician must make a reasonable guess on the diagnosis, the severity of the infection, and on the identity of the microorganism causing the disease (also known as a pathogen). Secondly, the clinician must make a reasonable guess on the susceptibility of the likely microorganisms(s) to the antimicrobials available for therapy, and based on these factors choose an appropriate empirical antimicrobial treatment (Mandell et al., 2010; Schaechter et al., 2007).

Empirical treatment is a medical term referring to the initiation of antimicrobial treatment prior to the determination of pathogen identity and antimicrobial susceptibility. Empirical treatment is often used when managing an infectious disease and can make the difference between cure and death for infected patients (Leibovici et al., 1998; Paul et al., 2010). The empirical treatment can be guided by a local institutional antibiogram (instABG) (Bax et al., 2001; Hindler and Stelling, 2007; Pakyz, 2007), also known as a "cumulative antibiogram report" (Hindler and Stelling, 2007). An instABG is generated from statistics on the locally tested combinations of pathogens and antimicrobials and thereby reflects the resistance level in the given population. From the instABG it can be read that, for example, the probability of *E. coli* being susceptible *in vitro* to cefuroxime is 71%.

Before an empirical treatment is administered, samples will be taken from the patient, usually both a blood sample and a "local" sample from the suspected site of infection, for example a urine sample if the patient is suspected of a urinary tract infection. Within a day or two bacteria are successfully isolated from blood or local samples in approximately 30% of the patients (Paul et al., 2006). Once isolated, the bacteria are

tested for their *in vitro* susceptibility to a set of antimicrobials. The simplest and most widely used method for antimicrobial susceptibility testing (AST) is the disc diffusion test, where bacteria are seeded onto an agar plate and paper discs impregnated with antimicrobials are placed over the surface. After incubation susceptibility to antimicrobials appear by clear areas around the disk and resistance is indicated as bacterial growth up to the discs. The diameter of the zone of inhibition by diffusion of the antimicrobial on to the agar plate is used to determine the susceptibility of the bacteria to the set of tested antimicrobials. Quantitative methods are also used to provide estimate of a minimum inhibitory concentration (MIC), a value that can be used to determine whether an effective antimicrobial concentration is attainable in body fluids. The lowest concentration of the antimicrobial agent that prevents visible growth, usually after an 18- 24-hour incubation period, is the MIC (Mandell et al., 2010; Schaechter et al., 2007).

The AST results from a bacterial isolate specify its susceptibility to each of the tested antimicrobials. The AST results can give reason to change the empirical treatment administered to the patient into a "final" treatment, where susceptibility to the antimicrobial treatment is confirmed by the AST. Due to the phenomenon of cross-susceptibility/resistance an AST result showing susceptibility to an antimicrobial often implies susceptibility to similar antimicrobials. Likewise, an AST result showing resistance to an antimicrobial often implies resistance to similar antimicrobials.

Factors specific to the patient suspected of infection must be considered to arrive at the optimal choice of antimicrobial treatment (Leibovici et al., 1999; Mandell et al., 2010). In this project, we addressed the following patient specific factors related to antimicrobial susceptibility:

1. **Nosocomiality (NOSO):** Patients with a Hospital-Acquired Infection (HAI) have a higher probability of being infected with resistant pathogens than patients with Community-Acquired Infections (CAI) (ECDC, 2017; Sanden et al., 2017).
2. **Prior Exposure (PE):** Patients recently exposed to antimicrobials have higher probability of subsequent increased bacterial resistance (Bell et al., 2014; Sanden et al., 2016).
3. **AST results:** Typically, AST results becomes available for a limited set of antimicrobials. When patient-specific AST results become available, and a treatment must be chosen, cross-resistance and cross-susceptibility for the untested treatments must be considered (Andreassen et al., 2015; Leclercq et al., 2013).

The aim of the project was to generate personalised ABGs, which predicts patient specific antimicrobial susceptibility in the hospital setting. During the project, we focused on making the research operational, by developing practical implementable

applications. The following chapters each present a step taken to generate personalised ABGs. These steps are shown on Figure 1.1.

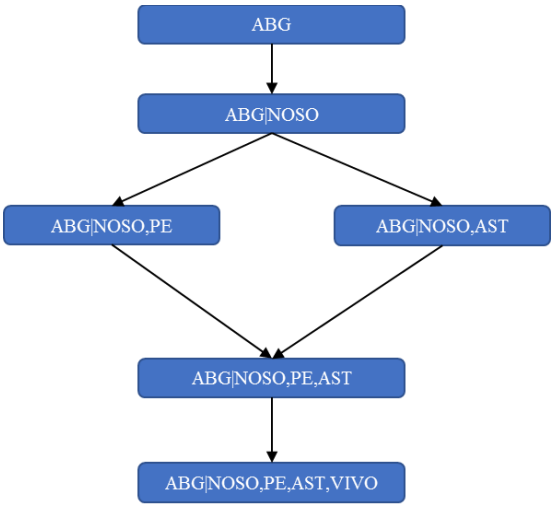


*Figure 1.1: Flow diagram showing the steps taken to generate personalised ABGs, starting with an institutional ABG, which was modified first by nosocomiality (NOSO). The resulting ABG|NOSO was then modified by prior antimicrobial exposure (PE) resulting in an ABG|NOSO,PE and by AST results resulting in an ABG|NOSO,AST. The ABG|NOSO,PE and the ABG|NOSO,AST were then combined. Finally, in vivo susceptibility modifications were made in the already existing system, TREAT Steward.*

**Chapter 2** provides of description of the work done to generate institutional ABGs accounting for nosocomiality. The first aim was to generate versions of the ABG|NOSO that represented community-acquired infections (ABG|CAI) and hospital-acquired infections (ABG|HAI), respectively. The second aim was to include evidence on cross-susceptibility/resistance in the ABGs, resulting in a crossABG|HAI and a crossABG|CAI. The crossABG was also a prerequisite for the approaches presented in Chapter 3 and Chapter 5.

**Chapter 3** is based primarily on Paper I. When AST results become available, it might give reason to adjust the expected susceptibility to antimicrobials for which susceptibility was not tested. The research objective was to develop and validate a method which uses cross-susceptibility/resistance to adjust an instABG with respect to AST results. The resulting personalised ABG is denoted ABG|AST.

**Chapter 4** is based primarily on Paper II. Bacteria from patients recently exposed to antimicrobials have an increased probability of being resistant to antimicrobials compared to those not recently exposed to antimicrobials. To generate ABGs for these patients by adjusting an instABG, a quantification of the increased resistance was needed. The research objective was to quantify the effect of prior antimicrobial exposure at patient level.

**Chapter 5** describes a method developed with the purpose of modifying the instABG to account for a patient's prior exposure (PE) to antimicrobials, where the resulting ABG is denoted ABG|PE. The chapter also serves as an operationalisation of Paper II. The content of this chapter is included in a patent application.

**Chapter 6** describes a method developed with the purpose of modifying the instABG to account for both PE and for AST results. The resulting ABG is denoted ABG|PE,AST. Like Chapter 5, the content of this chapter is also included in a patent application.

**Chapter 7** describes the implementation of the developed *in vitro* susceptibility modifications. The developed methods were implemented in TREAT Steward, a software solution for antimicrobial stewardship. The implementation is illustrated by going through a patient example.

These chapters and the included objectives are steps towards generating personalised ABGs, serving as a better starting point for antimicrobial treatment than an instABG. Thereby the project seeks to contribute to patient specific antimicrobial stewardship. The main findings, scientific contributions are discussed in **Chapter 8**, which also gives a conclusion and addresses future work.

# CHAPTER 2. INSTITUTIONAL ABGS

*To be able to generate personalised ABGs, we needed an instABG, which could be adjusted to patient specific factors. This chapter describes the approach used to generate an instABG from an isolate database, including the steps taken to ensure the quality of the isolate database. The chapter also describes how one of the patient specific factors, nosocomiality (NOSO), is taken into account by compiling two separate ABG|NOSO, one for community-acquired infections, the ABG|CAI and one for hospital-acquired infections, the ABG|HAI. Finally, the chapter describes the compilation of the cross-susceptibility and cross-resistance ABG, the crossABG of a given pathogen for pairs of antimicrobials. The crossABG is a prerequisite for the approaches presented in Chapter 3 and Chapter 5. Figure 2.1 shows the relation between the content of this chapter and the rest of the thesis.*

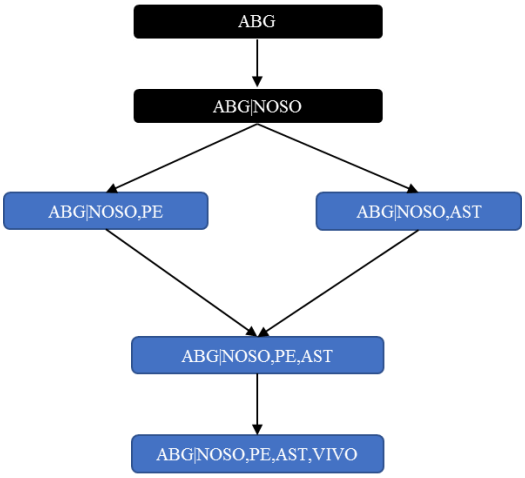


*Figure 2.1: This chapter describes the first steps taken to generate personalised ABGs, resulting in ABG|NOSO.*

The instABG is generated from statistics on the locally tested combinations of pathogens and antimicrobials and thereby reflects the resistance level for the patients in the institution. In the context of generating personalised ABGs, the instABG serves as our prior knowledge, which can be adjusted by patient specific factors. To illustrate the process of generating an ABG|HAI and ABG|CAI and the corresponding crossABG|HAI and crossABG|CAI, we will use a microbiological isolate database from Rambam Health Care Campus in Israel as an example. The database was compiled for the period 2012 to 2015 as part of a hospital specific calibration of the software solution for antimicrobial stewardship, TREAT Steward (Treat Systems ApS). When the ABGs were generated, as traditionally recommended, solely on the

basis of institutional AST results, some complications and limitations arose, which will be addressed in the following.

We divided the generation of an instABG into five steps, which will be described in the following sections:

**Step 1 – Quality-check of the isolate database:** The purpose of the first step was to ensure the quality of the isolate database, which contained AST results for the pathogens isolated from patient samples at the hospital's microbiological laboratory.

**Step 2 – Mapping reported species into pathogen groups:** The reported species were mapped into pathogen groups, to decrease the risk of estimating susceptibilities on the basis of a few, or even zero observed cases.

**Step 3 - Hospital and community ABGs:** The instABG was separated into an ABG representing hospital-acquired infections (ABG|HAI) and an ABG representing community-acquired infections (ABG|CAI).

**Step 4 – Filling in the gaps:** For many entries, both in the ABG|HAI and the ABG|CAI, few or no susceptibility results were available. We explored how to include more evidence in the ABG|HAI and ABG|CAI to fill in the empty entries.

**Step 5 – Including cross-resistance in the ABG:** The cross-susceptibility and cross-resistance observed in the isolate database were included in a crossABG|HAI and a crossABG|CAI. A similar crossABG will be used in Chapter 3 and Chapter 5.

## 2.1. QUALITY-CHECK OF THE ISOLATE DATABASE

The compiled isolate database from Rambam contained all AST results from *in vitro* isolated pathogens from all sample types (e.g. blood, urine, sputum). The database contained 44,557 patient- and episode-unique isolates. Examples are presented in Table 2.1. Each isolate was associated with information about:

- Isolate ID
- Patient ID (anonymised)
- Patient age
- Admission date of the patient
- Sample date (when the sample was taken)
- Sample type (blood or other)
- Species name
- AST results (susceptible=S, resistant=R or intermediate=I)

| IsolateID | PatientID | Age | Admission Date | Sample Date | Pathogen Name | Amikacin | Amoxicillin | Ampicillin | Cefazolin | Cefotaxime | Ceftazidime | Ceftriaxone | Cefuroxime |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 200150001 | 1572832 | 77 | 12/31/2011 | 1/1/2012 | Enterococcus faecalis | | | | | | | | |
| 200150004 | 1395133 | 24 | 1/1/2015 | 1/1/2015 | Escherichia coli | S | | R | | | S | S | S |
| 200150010 | 1407741 | 76 | 12/21/2013 | 12/21/2013 | Klebsiella pneumoniae ssp | R | | R | | | R | R | R |
| 200150011 | 1604350 | 47 | 12/31/2014 | 12/31/2014 | Enterobacter cloacae | S | | | | | S | S | R |

*Table 2.1: A segment of the data contained in the isolate database from Rambam.*

Isolates were selected for further analysis provided:

1. The first 6 columns containing Isolate ID, Patient ID, Patient age, Admission date, Sample date and Pathogen name were all filled in,
2. The patient's age was over 18 years,
3. Admission date was before the Sample date, and
4. The isolate was not a duplicate.

Two isolates were defined as duplicates if the isolates were from the same patient, had the same species name and the sample dates were separated by less than 30 days. To decide which one of the duplicates to be considered for deletion, a number of checks were performed. The duplicate to be deleted was identified by being:

- The isolate with the lowest number of AST results, or
- If the isolates had the same number of AST results: The least resistant isolate (fewest number of AST results = R), or
- If the two samples have identical AST results: The newest isolate.

A list of isolates with issues was constructed, i.e. a list of all isolates not satisfying one or more of the above criteria (Table 2.2). The list was used as a review tool where the reviewer could enter Yes or No in the "Delete isolate?" column and also enter a comment.

| Issue ID | Isolate ID | Mistakes description | Delete isolate? | Comment |
|---|---|---|---|---|
| **1** | 201226091 | Duplicate of isolate: 201225342 | Yes | |
| **2** | 201208437 | Duplicate of isolate: 201208305 | Yes | |
| **3** | 201208305 | Duplicate of isolate: 201213276 | Yes | |
| **4** | 201208437 | Duplicate of isolate: 201213276 | Yes | |

*Table 2.2: A segment of a list of isolates with identified issues.*

In total, we identified 10,129 issues that were added to the list. A review by a clinical expert from the institution had the purpose of identifying which issues should be deleted from the isolate database, and whether additional data could be provided in cases of missing data. After the review, all 10,129 isolates were deleted and the remaining 34,427 were selected for further analysis.

## 2.2. MAPPING SPECIES INTO PATHOGEN GROUPS

In the microbiological laboratory, the name of the identified species is reported for each isolate. Even though an isolate database may contain several thousand isolates like the Rambam database, some of the species do not occur frequently. As a consequence, the susceptibility for some pathogen/antimicrobial combinations must be decided on the basis of a few, or even zero observed cases. Since susceptibilities change over time, the problem cannot be solved by including susceptibility data for a longer period of time. It is recommended that clinical microbiology laboratories generate local ABGs with pathogen-specific susceptibility data annually, to optimise recommendations for empirical therapy (Mandell et al., 2010). Susceptibility data older than three years should definitely be used with caution. To get higher isolate counts, it may be useful to construct an ABG|HAI and an ABG|CAI for groups of pathogens, where each pathogen group may contain one or more species. If the groups are carefully defined the loss of species resolution caused by the grouping may be more than compensated for by the reduction in statistical noise caused by the higher counts, thus providing an overall improved accuracy of the estimates of susceptibility (Andreassen et al., 2009).

In the isolate database from Rambam, we found 285 different species names. The reporting of species names was not standardised, and therefore there the 285 different names may not truly reflect 285 different types of species. Table 2.3 shows the mapping of species into pathogen groups for the Rambam database, where the reported species names were mapped into 27 pathogen groups. The mapping was approved by a local expert. Even though the grouping of species provided higher isolate counts, some groups were still represented by sparse susceptibility data with

counts smaller than 20 (Campylobacter, HACEK, Listeria, Meningococcus, Moraxella, and Streptococcus group D).

| **Pathogen group** | **Species reported from institutional laboratory** | |
|---|---|---|
| Acinetobacter (N = 1278) | *Acinetobacter baumannii*<br>*Acinetobacter calcoaceticus*<br>*Acinetobacter haemolyticus*<br>*Acinetobacter johnsonii*<br>*Acinetobacter junii*<br>*Acinetobacter lwoffii* | *Acinetobacter radioresistens*<br>*Acinetobacter spp*<br>*Acinetobacter ursingii*<br>*Nocardia brasiliensis*<br>*Nocardia spp*<br>*Streptomyces species* |
| Campylobacter (N = 15) | *Campylobacter fetus*<br>*Campylobacter jejuni* | *Campylobacter spp* |
| Candida (N = 161) | *Aspergillus flavus*<br>*Aspergillus fumigatus*<br>*Aspergillus Niger*<br>*Aspergillus terreus*<br>*Candida albicans*<br>*Candida dubliniensis*<br>*Candida glabrata*<br>*Candida krusei* | *Candida parapsilosis*<br>*Candida pelliculosa*<br>*Candida species,not albicans*<br>*Candida tropicalis*<br>*Fusarium spp*<br>*Mould fungus*<br>*Saccharomyces cerevisiae* |
| Citrobacter (N = 788) | *Citrobacter amalonaticus*<br>*Citrobacter braakii*<br>*Citrobacter farmeri*<br>*Citrobacter freundii*<br>*Citrobacter koseri* | *Citrobacter koseri (C. diversus)*<br>*Citrobacter sedlakii*<br>*Citrobacter spp*<br>*Citrobacter youngae* |
| Escherichia coli (N = 8563) | *Escherichia coli*<br>*Escherichia fergusonii* | *Escherichia hermannii* |
| Enterobacter (N = 1199) | *Enterobacter aerogenes*<br>*Enterobacter amnigenus*<br>*Enterobacter asburiae* | *Enterobacter cloacae*<br>*Enterobacter gergoviae*<br>*Enterobacter species* |
| Enterococcus (N = 4348) | *Enterococcus avium*<br>*Enterococcus casseliflavus*<br>*Enterococcus durans*<br>*Enterococcus faecalis*<br>*Enterococcus faecium* | *Enterococcus gallinarum*<br>*Enterococcus hirae*<br>*Enterococcus raffinosus*<br>*Enterococcus spp* |
| Gram Negative Anaerobe (N = 213) | *Anaerobic gram negative rods*<br>*Anaerobic gram positive rod*<br>*Bacteroidas ovatus*<br>*Bacteroides caccae*<br>*Bacteroides distasonis*<br>*Bacteroides fragilis*<br>*Bacteroides spp*<br>*Bacteroides stercoris*<br>*Bacteroides thetaiotaomicron*<br>*Bacteroides uniformis*<br>*Bacteroides vulgatus* | *Fusobacterium mortiferum*<br>*Fusobacterium nucleatum*<br>*Fusobacterium spp*<br>*Prevotella bivia*<br>*Prevotella intermedia*<br>*Prevotella melaninogenica*<br>*Prevotella oralis*<br>*Prevotella oris*<br>*Prevotella species (non-pigmented group)*<br>*Prevotella species (pigmented group)*<br>*Veillonella parvula* |

| | | |
|---|---|---|
| | *Delftia acidovorans* | *Veillonella spp* |
| Gram Positive Anaerobe (N = 95) | *Actinomyces meyeri*<br>*Actinomyces naeslundii*<br>*Actinomyces spp*<br>*Anaerobic gram positive coccus*<br>*Arcanobacterium haemolyticum*<br>*Clospridium spp*<br>*Clostridium barati*<br>*Clostridium clostridiiforme*<br>*Clostridium paraputrificum*<br>*Clostridium perfringens*<br>*Clostridium septicum*<br>*Clostridium sordellii* | *Clostridium spp*<br>*Clostridium subterminale*<br>*Eubacterium lentum*<br>*Eubacterium spp*<br>*Peptococcus sp.*<br>*Peptostreptococcus anaerobius*<br>*Peptostreptococcus asaccharolyticus*<br>*Peptostreptococcus micros*<br>*Peptostreptococcus sp.*<br>*Propionibacterium acnes*<br>*Propionibacterium species*<br>*Rothia mucilaginosa* |
| Gram Positive Rods (N = 64) | *Bacillus species*<br>*Bacillus subtilis (globigii)*<br>*Corynebacterium amycolatum*<br>*Corynebacterium jeikeium group*<br>*Corynebacterium minutissimum*<br>*Corynebacterium pseudodiphteriticum* | *Corynebacterium species*<br>*Corynebacterium stariatum*<br>*Corynebacterium urealyticum*<br>*Cryptococcus neoformans*<br>*Erysipelothrix rhusiopathiae*<br>*Gram positive bacilli* |
| HACEK (N = 3) | *Eikenella corrodens* | |
| Haemophilus (N = 329) | *+Haemophilus influenza beta lact*<br>*-Haemophilus influenza beta lact*<br>*Haemophilus influenza invasive* | *Haemophilus influenzae*<br>*Haemophilus parainfluenzae*<br>*Haemophilus spp* |
| Klebsiella (N = 4469) | *Klebsiella oxytoca*<br>*Klebsiella oxytoca/(Raoultella planticola/terrigena)*<br>*Klebsiella pneumoniae*<br>*Klebsiella pneumoniae ssp ozaenae* | *Klebsiella pneumoniae ssp pneumoniae*<br>*Klebsiella pneumoniae ssp pneumoniae/(R.planticola/terrig.)*<br>*Klebsiella spp* |
| Listeria (N = 10) | *Listeria monocytogenes* | *Listeria species* |
| Meningococcus (N = 1) | *Neisseria meningitidis* | |
| Moraxella (N = 10) | *Moraxella group* | *Moraxella osloensis* |
| Other Gram Negative (N = 943) | *Achromobacter xylosoxidans ssp denitrificans*<br>*Achromobacter xylosoxidans ssp xylosoxidans*<br>*Aeromonas hydrophila/caviae*<br>*Aeromonas salmonicida*<br>*Aeromonas sobria*<br>*Aeromonas spp*<br>*Aeromonas veronii biovar veronii*<br>*Alcaligenes faecalis ssp faecalis*<br>*Bordetella bronchiseptica* | *Kluyvera cryocrescens*<br>*Kluyvera species*<br>*Neisseria cinerea*<br>*Neisseria gonorrhoeae*<br>*Neisseria spp*<br>*Nonfermenting Gram-Negative Bacillus*<br>*Ochrobactrum anthropi*<br>*Pantoea agglomerans (formerly enterobacter agglomerans)*<br>*Pantoea spp* |

| | | |
|---|---|---|
| | *Branhamella catarrhalis* | *Pasteurella multocida* |
| | *Brevundimonas diminuta* | *Pasteurella pneumotropica* |
| | *Brevundimonas diminuta/vesicularis* | *Pasteurella spp* |
| | *Brucella melitensis* | *Prevotella disiens* |
| | *Brucella melitensis complement* | *Rahnella aquatilis* |
| | *Burkholderia cepacia* | *Raoultella ornithinolytica* |
| | *Burkholderia cepacia group* | *Raoultella planticola* |
| | *Burkholderia gladioli* | *Rhizobium radiobacter* |
| | *Cedecea davisae* | *Serratia ficaria* |
| | *Chryseobacterium gleum* | *Serratia fonticola* |
| | *Chryseobacterium indologenes* | *Serratia liquefaciens* |
| | *Chryseobacterium meningosepticum* | *Serratia liquefaciens group* |
| | *Comamonas testosteroni* | *Serratia marcescens* |
| | *Ewingella americana* | *Serratia odorifera* |
| | *Finegoldia magna* | *Serratia plymuthica* |
| | *Gardnerella vaginalis* | *Serratia rubidaea* |
| | *Globicatella sanguinis* | *Serratia species* |
| | *Gram negative bacilli* | *Shewanella putrefaciens group* |
| | *Gram negative coccobacilli* | *Sphingobacterium spiritivorum* |
| | *Granulicatella adiacens* | *Sphingobacterium thalpophilum* |
| | *Granulicatella elegans* | *Sphingomonas paucimobilis* |
| | *Hafnia alvei* | *Stenotrophomonas maltophilia* |
| Pneumococcus (N = 215) | *Streptococcus pneumoniae* | |
| Proteus (N = 2818) | *Morganella morganii* | *Proteus vulgaris group* |
| | *Morganella morganii ssp morganii* | *Proteus vulgaris group/Proteus penneri* |
| | *Morganella morganii ssp sibonii* | *Providencia alcalifaciens* |
| | *Proteus mirabilis* | *Providencia rettgeri* |
| | *Proteus penneri* | *Providencia species* |
| | *Proteus species* | *Providencia stuartii* |
| Pseudomonas (N = 215) | *Pseudomonas aeruginosa* | *Pseudomonas pseudoalcaligenes* |
| | *Pseudomonas fluorescens* | *Pseudomonas putida* |
| | *Pseudomonas luteola* | *Pseudomonas spp* |
| | *Pseudomonas mendocina* | *Pseudomonas stutzeri* |
| | *Pseudomonas oryzihabitans* | |
| Salmonella non typhi (N = 44) | *Salmonella enteritidis* | *Salmonella spp* |
| | *Salmonella group* | |
| Staphylococcus - Coagulase negative (N = 1437) | *Coagulase negative Staphylococcus* | *Staphylococcus hominis ssp hominis* |
| | *Micrococcus luteus / lylae* | *Staphylococcus hyicus* |
| | *Micrococcus species* | *Staphylococcus intermedius* |
| | *Staphylococcus auricularis* | *Staphylococcus lentus* |
| | *Staphylococcus capitis* | *Staphylococcus lugdunensis* |
| | *Staphylococcus caprae* | *Staphylococcus saccharolyticus* |
| | *Staphylococcus chromogenes* | *Staphylococcus saprophyticus* |
| | *Staphylococcus cohnii ssp cohnii* | *Staphylococcus schleiferi* |
| | *Staphylococcus cohnii ssp urealyticum* | *Staphylococcus sciuri* |

| | | |
|---|---|---|
| | *Staphylococcus epidermidis*<br>*Staphylococcus haemolyticus*<br>*Staphylococcus hominis* | *Staphylococcus simulans*<br>*Staphylococcus warneri*<br>*Staphylococcus xylosus* |
| Staphylococcus - Coagulase positive (N = 2973) | *Gram positive cocci consistent with Staphylococcus* | *Staphylococcus aureus* |
| Streptococcus group A (N=24) | *Streptococcus pyogenes (group A)* | |
| Streptococcus group B (N = 434) | *Streptococcus agalactiae (Group B)* | *Streptococcus group B* |
| Streptococcus group D (N = 16) | *Streptococcus alactolyticus*<br>*Streptococcus gallolyticus* | *Streptococcus gallolyticus ssp gallolyticus*<br>*Streptococcus gordonii* |
| Streptococcus viridans (N = 259) | *Alpha haemolytic Streptococcus*<br>*Gemella morbillorum*<br>*Streptococcus parasanguinis*<br>*Streptococcus infantarius ssp coli*<br>*Streptococcus mitis/oralis/*<br>*Streptococcus mitis/Streptococcus oralis*<br>*Streptococcus mutans*<br>*Streptococcus pasteurianus* | *Streptococcus pluranimalium*<br>*Streptococcus salivarius*<br>*Streptococcus sanguis*<br>*Streptococcus spp*<br>*Streptococcus vestibularis*<br>*Streptococcus viridans group* |
| Streptococcus (N = 137) | *Aerococcus viridans*<br>*Str.dys.dysgalactiae/Str.dys.equisimilis*<br>*Streptococcus anginosus*<br>*Streptococcus canis*<br>*Streptococcus constellatus*<br>*Streptococcus constellatus (viridans strep)*<br>*Streptococcus constellatus ssp pharyngis*<br>*Streptococcus dysgalactiae ssp dysgalactiae* | *Streptococcus dysgalactiae ssp equisimilis*<br>*Streptococcus group C*<br>*Streptococcus group F*<br>*Streptococcus group G*<br>*Streptococcus intermedius*<br>*Streptococcus thermophilus*<br>*Streptococcus thoraltensis* |

*Table 2.3: The mapping of species into pathogen groups for the Rambam database.*

As an example, Table 2.4 shows the last pathogen group from Table 2.3, *streptococcus*. It can be seen, that only 2 out of 15 reported species were isolated more than 20 times. For the majority of the reported species in this group, the small number of isolates are not useful to compile a species-specific susceptibility profile in an instABG. When segregating the isolates into those representing HAIs and CAIs, the number of isolates in each group are further reduced. In section 2.4 we explore how to include more evidence in the ABG|HAI and ABG|CAI, than what can be achieved by using statistics on institutional AST results.

| The streptococcus pathogen group | N |
|---|---|
| *Aerococcus viridans* | 8 |
| *Str.dys.dysgalactiae/Str.dys.equisimilis* | 4 |
| *Streptococcus anginosus* | 56 |
| *Streptococcus canis* | 1 |
| *Streptococcus constellatus* | 9 |
| *Streptococcus constellatus (viridans strep)* | 2 |
| *Streptococcus constellatus ssp pharyngis* | 5 |
| *Streptococcus dysgalactiae ssp dysgalactiae* | 2 |
| *Streptococcus dysgalactiae ssp equisimilis* | 25 |
| *Streptococcus group C* | 1 |
| *Streptococcus group F* | 2 |
| *Streptococcus group G* | 3 |
| *Streptococcus intermedius* | 15 |
| *Streptococcus thermophilus* | 3 |
| *Streptococcus thoraltensis* | 1 |
| **Total number of streptococcus isolates** | 137 |

*Table 2.4: The number of isolates in the streptococcus pathogen group.*

## 2.3. HOSPITAL AND COMMUNITY ABGS

One of the patient specific factors that the ABG can be adjusted for is nosocomiality, i.e. whether the infection is hospital-acquired or community-acquired. The high rates of antimicrobial resistance in hospitals has been associated with high rates of antimicrobial use (Doron and Davidson, 2011). Patients with hospital-acquired infections therefore have a higher probability of being infected with resistant pathogens than patients that have acquired an infection elsewhere. This gives reason to compile an ABG|HAI for hospital-acquired infections (HAI) and an ABG|CAI for community-acquired infections (CAI). The effect of higher resistance in HAIs has been shown to be sufficiently expressed in infections acquired after at least 7 days in hospital, to be used to generate hospital specific ABGs (Dickstein et al., 2016). Throughout the thesis, we will use three versions of the instABG, which were defined as follows:

**The ABG|CAI** included isolates from samples drawn *before* a patient had spent 7 days in hospital. Thereby the ABG|CAI mainly represents patients, who had community-acquired infections, but isolates from patients coming from other healthcare facilities than the hospital (e.g. nursing home) could also be included.

**The ABG|HAI** included isolates from samples drawn *after* a patient had spent 7 days in hospital. The ABG|HAI thereby represents patients, who had hospital-acquired infections.

**The instABG** included the total patient population represented in the isolate database from the microbiological laboratory. The instABG thereby included both the ABG|HAI and the ABG|CAI.

Table 2.5 shows the antimicrobial specific susceptibilities for biggest pathogen group, *E. coli*, in the three versions of the ABG. It can be seen, for example, that the probability of an *E. coli* isolate being susceptible to cefuroxime is 71.2% in CAIs and 49.6% in HAIs.

| **Pathogen: *E. coli*** | **Probability of susceptibility** | | |
|---|---|---|---|
| **Antimicrobial** | instABG | ABG\|CAI | ABG\|HAI |
| Ampicillin | 25.2% | 26.6% | 13.4% |
| Piperacillin | 31.6% | 32.4% | 25.0% |
| Amoxicillin-clavulanate | 78.3% | 80.0% | 63.0% |
| Piperacillin-tazobactam | 92.9% | 93.6% | 86.8% |
| Cefazolin | 50.0% | 53.2% | 28.6% |
| Cefuroxime | 68.9% | 71.2% | 49.6% |
| Ceftazidime | 72.7% | 74.8% | 55.1% |
| Ceftriaxone | 72.8% | 74.9% | 55.3% |
| Meropenem | 99.7% | 99.8% | 99.0% |
| Ertapenem | 99.7% | 99.8% | 99.1% |
| Imipenem-cilastatin | 99.7% | 99.8% | 99.4% |
| Aztreonam | 41.5% | 36.2% | 55.6% |
| Doxycycline | 45.4% | 47.3% | 30.0% |
| Gentamicin | 81.1% | 82.5% | 69.1% |
| Amikacin | 99.5% | 99.7% | 98.3% |
| Ofloxacin | 57.2% | 58.1% | 47.3% |
| Ciprofloxacin | 57.5% | 59.3% | 41.9% |
| Nitrofurantoin | 95.8% | 95.8% | 96.4% |
| Fosfomycin | 99.1% | 99.1% | 98.6% |
| Sulfa-trimethoprim | 54.2% | 55.7% | 41.5% |
| Chloramphenicol | 90.3% | 89.3% | 95.7% |

*Table 2.5: Probability of susceptibility in E. coli isolates.*

We compared the susceptibility levels in the ABG|HAI and the ABG|CAI (Sanden et al., 2017). The differences in resistance levels were calculated as odds ratios (ORs) with 95% confidence intervals (CI) for resistance. The results presented in the following are mainly based on a conference abstract (ECCMID 2017)(Sanden et al., 2017).

Figure 2.2 shows the difference in the susceptibility data from HAI and CAI for the pathogen group with the highest number of AST results, *E. coli* ($N_{AST}$ = 113,791). As expected, *E. coli* showed significantly higher resistance to most antimicrobials (16 out of the 21 antimicrobials) in HAIs compared to resistance in CAIs. This included significantly higher resistance in HAIs for all penicillins (ORs: 2.2-2.4), cephalosporins (ORs: 2.4-2.8), aminoglycosides (ORs: 2.1-5.1), and quinolones (ORs: 1.5-2.0).

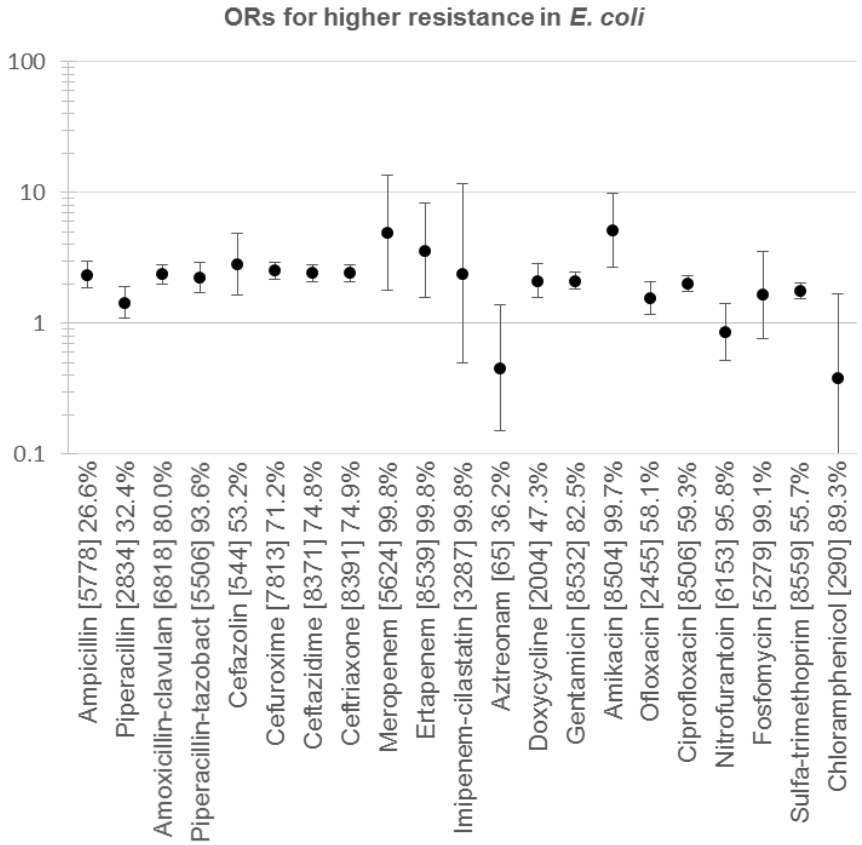


*Figure 2.2: ORs for higher resistance in E. coli isolates from patients with HAI compared to CAI. Each antimicrobial is presented with [Number of AST results] and the percentage of susceptible isolates from CAI.*

Table 2.6 shows the nine pathogen groups with the highest number of AST results across all tested antimicrobials in the database. These pathogen groups represent a sum of 320,010 AST results or 92% of all AST results. All pathogen groups had significant ORs for increased resistance in HAI isolates ranging from 1.3 to 4.0. The largest difference in resistance between bacteria isolated from HAIs and bacteria isolated CAIs was observed for *Acinetobacter*, which is a typical pathogen for HAIs, but not in the community.

| Pathogen group | $N_{AST}$ (%HAI) | OR (95% CI) |
|---|---|---|
| *Acinetobacter* | 11,031 (51%) | 4.0 (3.7-4.3) |
| *Staph. coag. pos.* | 25,620 (24%) | 2.6 (2.4-2.8) |
| *Staph. coag. neg.* | 11,852 (20%) | 2.1 (1.9-2.3) |
| *Klebsiella* | 58,499 (25%) | 2.1 (2.0-2.2) |
| *Enterococcus* | 17,292 (19%) | 1.8 (1.7-2.0) |
| *E. coli* | 113,791 (10%) | 1.7 (1.7-1.8) |
| *Pseudomonas* | 30,500 (39%) | 1.6 (1.5-1.7) |
| *Proteus* | 36,588 (24%) | 1.5 (1.4-1.6) |
| *Enterobacter* | 14,837 (23%) | 1.3 (1.2-1.4) |
| All pathogen groups | 343,761 (21%) | 1.94 (1.87-1.94) |
| Gram- pathogen groups | 286,098 (21%) | 1.87 (1.84-1.91) |
| Gram+ pathogen groups | 56,877 (21%) | 2.24 (2.14-2.34) |

*Table 2.6: ORs for higher resistance in HAI compared to CAI.*

As expected we observed a significant difference in resistance level in the susceptibilities from the ABG|HAI and the ABG|CAI. The results emphasise the importance of personalising the instABG with respect to HAI and CAI.

## 2.4. FILLING IN THE GAPS IN THE ABGS

The ABG|HAI and ABG|CAI from Rambam each included 27 pathogen groups and 55 antimicrobials, giving a total number of 27*55 = 1485 entries in each of these ABGs. Table 2.7 shows a segment of the AST results used in the ABG|HAI. Many of the entries remained empty or only contained a few results (coloured red). By using the statistics from pathogen/antimicrobial combinations with >10 AST results it was possible to fill in 213 (15%) of the 1485 entries in the ABG|HAI and 265 (18%) of the entries in the ABG|CAI.

| **HAI statistics** | | **Pathogen** | | |
|---|---|---|---|---|
| Antimicrobial | AST result | *Acinetobacter* | *E. coli* | *Streptococcus* |
| **Penicillin** | S | 0 | 0 | 8 |
| J01CE01 | R | 0 | 0 | 0 |
| **Cloxacillin** | S | 0 | 0 | 0 |
| J01CF02 | R | 0 | 0 | 0 |
| **Oxacillin** | S | 0 | 0 | 0 |
| J01CF04 | R | 0 | 0 | 0 |
| **Ampicillin-sulbactam** | S | 267 | 0 | 0 |
| J01CR01 | R | 257 | 0 | 0 |
| **Amoxicillin-clavulanate** | S | 0 | 427 | 0 |
| J01CR02 | R | 0 | 251 | 0 |
| **Piperacillin-tazobactam** | S | 52 | 488 | 0 |
| J01CR05 | R | 567 | 74 | 0 |
| **Cefalexin** | S | 0 | 0 | 0 |
| J01DB01 | R | 0 | 0 | 0 |
| **Cefazolin** | S | 0 | 20 | 0 |
| J01DB04 | R | 0 | 50 | 0 |
| **Cefuroxime** | S | 0 | 412 | 0 |
| J01DC02 | R | 0 | 418 | 0 |

*Table 2.7: A segment of the AST results used in the ABG|HAI.*

For the ABG to be used as a guidance for the choice of antimicrobial therapy both for clinicians and for decision support systems, all entries must be filled in. Although the susceptibility is usually tested to antimicrobials which are likely to be chosen for therapy, it may be necessary to use an antimicrobial, for which few or no susceptibility results are available in the ABG|HAI or ABG|CAI.

### 2.4.1. INCLUDING PRIOR DISTRIBUTIONS

To fill in the empty entries in the ABG we explored how to include more evidence in the ABG|HAI and ABG|CAI, than what can be achieved by using statistics on institutional AST results. This additional evidence may, in the Bayesian tradition, be considered prior information, i.e. prior to the statistical processing of the institutional AST results. This evidence can be expressed as (prior) probability distributions, for example based on:

- Susceptibility data from another period of time
- Susceptibility data from another institution
- Opinions from clinical experts
- Observations from the literature

The probabilities derived from these sources are expressed as Dirichlet counts. For example, the prior opinion derived from one of these sources may be that the

probability of susceptibility of *E. coli* to cefuroxime is 80%. This may be expressed as 8 imaginary "Dirichlet observations" in the isolate database of susceptibility and 2 observations of resistance. A convenient property of this way of expressing prior opinions is that the Bayesian posterior probability is very simple to calculate. The Dirichlet observations are simply added to any real observations in the isolate database (Spiegelhalter et al., 1993). For example, if the isolate database contains 100 observations of the susceptibility of *E. coli* to cefuroxime, 71 (71%) showing susceptibility and 29 (29%) showing resistance then the posterior probability of susceptibility would be (8 + 71) / (8+ 71 + 2 + 29) = 72% (Table 2.8). This is close to the 71% observed in the isolate database. Had the number of Dirichlet observations been 1000, 800 observation of susceptibility and 200 of resistance, then the resulting posterior would have been 79%. This is close to the prior opinion and this example illustrates that the number of imaginary Dirichlet observation can be used to indicate the strength of the prior opinion; A large Dirichlet count (1000) indicating a strong prior opinion and a small Dirichlet count (10) indicating a weak prior opinion.

| **Pathogen: *E. coli*** | Antimicrobial | AST result | RAM2015 | Prior opinion | Coverage |
|---|---|---|---|---|---|
| Weak prior opinion | **Cefuroxime** J01DC02 | S | 71 | 8 | 72% |
| | | R | 29 | 2 | |
| Strong prior opinion | **Cefuroxime** J01DC02 | S | 71 | 800 | 79% |
| | | R | 29 | 200 | |

*Table 2.8: An example of the use of Dirichlet observations.*

To generate an ABG|HAI and ABG|CAI for Rambam, we included the following prior distributions:

**Susceptibility data from another institution**: We included an instABG generated at another Israeli hospital. The instABG was compiled at Beilinson Hospital at Rabin Medical Center and contained susceptibility data from the period 2011-2014. A segment of the susceptibility data used from this instABG is shown in the column "Rab2014" in Table 2.9. Counts from the Rab2014 instABG were downscaled to give a sum of 10. In this way, the contribution of these counts depends on the number of AST results in the currently assessed database (Ram2015). The higher the counts from the new isolate database, the smaller the weight from the prior results on the aggregated probability of susceptibility ("Coverage").

**Opinions from clinical experts**: We included expert opinions on the level of susceptibility suggested by clinical experts at Beilinson Hospital (Rabin Medical Center) in 2014. These opinions were expressed as statistical counts and examples are shown in the column "Prior opinion" in Table 2.9.

**Observations from the literature**: EUCAST (The European Committee on Antimicrobial Susceptibility Testing) has designed a set of rules on intrinsic resistance and exceptional phenotypes (EUCAST, 2016). EUCAST expert rules on intrinsic resistance were expressed as S=0 and R=1000, giving a coverage of 0%. EUCAST expert rules on resistance of exceptional phenotypes were expressed as S =1000 and R=0, giving a coverage of 100%. These counts were included in the column "Prior opinion" in Table 2.9.

Table 2.9 shows a segment of these distributions for *E. coli*, alongside the statistics from the current isolate database, all expressed as statistical counts on susceptibility versus resistance. We will come back to the column "New opinion" in the next section.

| **HAI statistics** | | *Pathogen:* ***E. coli*** | | | | |
|---|---|---|---|---|---|---|
| Antimicrobial | AST result | RAM2015 | RAB2014 | Prior opinion | New opinion | Coverage |
| **Ampicillin-sulbactam** | S | 0 | 4.8 | 39.8 | | 41% |
| J01CR01 | R | 0 | 5.2 | 60.2 | | |
| **Amoxicillin-clavulanate** | S | 427 | 6.9 | 45.1 | | 61% |
| J01CR02 | R | 251 | 3.1 | 54.9 | | |
| **Piperacillin-tazobactam** | S | 488 | 9.6 | 82.5 | | 86% |
| J01CR05 | R | 74 | 0.4 | 17.5 | | |
| **Cefalexin** | S | 0 | 6.4 | 0 | | 1% |
| J01DB01 | R | 0 | 3.7 | 1000 | | |
| **Cefazolin** | S | 20 | 0 | 20 | | 24% |
| J01DB04 | R | 50 | 0 | 80 | | |
| **Cefuroxime** | S | 412 | 6.4 | 51.7 | | 50% |
| J01DC02 | R | 418 | 3.6 | 48.3 | | |

*Table 2.9: A segment of the statistical distributions for E. coli in HAIs.*

### 2.4.2. REVIEW AND NEW OPINIONS

Now with the distributions available, the next step towards a final ABG was to get the susceptibility data, representing our current posterior belief, reviewed by a clinical expert from the institution. This was done to get input about local susceptibilities, which were not reflected in the available statistical counts. The column "New opinion" was used to handle this process where the reviewer could enter opinions expressed as statistical counts (Table 2.10).

| **HAI statistics** | | ***Pathogen: E. coli*** | | | | |
|---|---|---|---|---|---|---|
| Antimicrobial | AST result | RAM2015 | RAB2014 | Prior opinion | New opinion | Coverage |
| **Ampicillin-sulbactam** | S | 0 | 4.8 | 39.8 | 428 | 60% |
| J01CR01 | R | 0 | 5.2 | 60.2 | 252 | |
| **Amoxicillin-clavulanate** | S | 427 | 6.9 | 45.1 | 427 | 62% |
| J01CR02 | R | 251 | 3.1 | 54.9 | 251 | |
| **Piperacillin-tazobactam** | S | 488 | 9.6 | 82.5 | 488 | 87% |
| J01CR05 | R | 74 | 0.4 | 17.5 | 74 | |
| **Cefalexin** | S | 0 | 6.4 | 0 | 20 | 2% |
| J01DB01 | R | 0 | 3.7 | 0 | 51 | |
| **Cefazolin** | S | 20 | 0 | 20 | 20 | 25% |
| J01DB04 | R | 50 | 0 | 80 | 50 | |
| **Cefuroxime** | S | 412 | 6.4 | 51.7 | 412 | 50% |
| J01DC02 | R | 418 | 3.6 | 48.3 | 418 | |

*Table 2.10: A segment of the review tool with statistical distributions for E. coli in HAIs.*

As a helping tool to draw the reviewer's attention to cases with divergent statistics, we highlighted the cells:

- Green shading indicated a significant difference in susceptibility counts between the RAM2015 and the RAB2014 statistics.
- Yellow shading indicated a difference between the prior opinion and the total counts from the RAM2015 and the RAB2014 statistics.
- Red shading indicated if new opinions deviated significantly from the sum of the other three columns.

The resulting column "Coverage" in Table 2.10 now shows a segment of the final coverages used in the ABG|HAI for *E. coli.* The coverage was calculated as the sum of the three distributions and expressed as the probability of susceptibility. For example, the probability of an *E. coli* isolate being susceptible to ampicillin-sulbactam is (4.8 + 39.8 + 428) / (4.8 + 39.8 + 428 + 5.2 + 60.2 + 252) = 60%.

## 2.5. INCLUDING CROSS-SUSCEPTIBILITY/RESISTANCE IN THE ABG

Susceptibility to an antimicrobial often implies susceptibility to similar antimicrobials and resistance to an antimicrobial often implies resistance to similar antimicrobials. When patient specific AST results become available, we can use knowledge on cross-susceptibility/resistance as an indicator for whether to expect susceptibility or resistance to antimicrobials for which no AST results are available.

This activity is known as interpretative reading of the ABG (Courvalin, 1996; Leclercq et al., 2013) In Chapter 3 and Chapter 5, we explore approaches of interpretative reading. In these approaches, we used a crossAGB, which contained statistics on cross-susceptibility/resistance between pairs of antimicrobials for each pathogen group.

Table 2.11 shows an example of the statistical data on cross-susceptibility/resistance that can be obtained from an isolate database, in this case on *E. coli* isolates in HAIs from Rambam 2012-2015. Some of the antimicrobials and antimicrobial combinations have zero AST results ("0"), and thereby no data which can be used to calculate the level of cross-susceptibility/resistance.

| **HAI statistics**<br>Pathogen: *E. coli* | | | **Cefuroxime** J01DC02 | | **Cefotaxime** J01DD01 | | **Ceftazidime** J01DD02 | |
|---|---|---|---|---|---|---|---|---|
| Antimicrobial | AST statistics | | S | R | S | R | S | R |
| **Ampicillin-sulbactam** | S | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| J01CR01 | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Amoxicillin-clavulanate** | S | 427 | 317 | 85 | 0 | 0 | 335 | 83 |
| J01CR02 | R | 251 | 28 | 201 | 0 | 0 | 52 | 188 |
| **Piperacillin-tazobactam** | S | 488 | 254 | 187 | 0 | 0 | 295 | 177 |
| J01CR05 | R | 74 | 13 | 52 | 0 | 0 | 25 | 46 |

*Table 2.11: An example of the data on cross-susceptibility/resistance that can be obtained from an isolate database.*

From the data given in Table 2.11 we can for example calculate the probability of susceptibility to amoxicillin-clavulanate, which is denoted P(amoCl) as:

P(amoCl) = 427 / (427+251) = 0.63 = 63%.

The conditional probability of susceptibility to amoCl given susceptibility to cefuroxime (cefur) is denoted P(amoCl|cefur) and is calculated as:

P(amoCl|cefur) = 317/ (317+28) = 0.92 = 92%

The OR for increased susceptibility to amoCl given susceptibility to cefur is calculated as:

$$OR_{amoCl|cefur} = \frac{OD_{amoCl|cefur}}{OD_{amoCl}} = \frac{P(amoCl|cefur)}{1-P(amoCl|cefur)} \frac{1-P(amoCl)}{P(amoCl)} = \frac{0.92}{0.08} \frac{0.37}{0.63} = 6.7$$

(These probabilities can be found in Table 2.12)

If we then consider susceptibility to amoCl given resistance to cefur, denoted P(amoCl|¬cefur), only 85 (30%) out of 286 isolates were susceptible to amoCl, with the corresponding OR = 0.2. In this example, an AST result on cefuroxime would be a useful indicator for whether or not amoCl could be expected to cover an *E. coli* infection, even if the susceptibility to amoCl had not been tested itself.

Table 2.12 shows a segment of a compiled crossABG|HAI for *E. coli* where the conditional probabilities and ORs of susceptibility are included for the antimicrobial listed on the left. Cases with a conditional probability of 100% gives an OR = ∞. We get a conditional probability of 100% when we calculate an antimicrobial's cross-susceptibility to itself (cefur in Table 2.12).

| **HAI statistics**<br>Pathogen: *E. coli* | | | **Cefuroxime** J01DC02 | | **Cefotaxime** J01DD01 | | **Ceftazidime** J01DD02 | |
|---|---|---|---|---|---|---|---|---|
| Antimicrobial | AST statistics | | S | R | S | R | S | R |
| **Ampicillin-sulbactam**<br>J01CR01 | S | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Coverage | ? | ? | ? | ? | ? | ? | ? |
| | Odds ratio | | ? | ? | ? | ? | ? | ? |
| **Amoxicillin-clavulanate**<br>J01CR02 | S | 427 | 317 | 85 | 0 | 0 | 335 | 83 |
| | R | 251 | 28 | 201 | 0 | 0 | 52 | 188 |
| | Coverage | **63%** | **92%** | 30% | ? | ? | 87% | 31% |
| | Odds ratio | | 6.7 | 0.2 | ? | ? | 3.8 | 0.3 |
| **Piperacillin-tazobactam**<br>J01CR05 | S | 488 | 254 | 187 | 0 | 0 | 295 | 177 |
| | R | 74 | 13 | 52 | 0 | 0 | 25 | 46 |
| | Coverage | 87% | 95% | 78% | ? | ? | 92% | 79% |
| | Odds ratio | | 3.0 | 0.5 | ? | ? | 1.8 | 0.6 |
| **Cefalexin**<br>J01DB01 | S | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | R | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Coverage | ? | ? | ? | ? | ? | ? | ? |
| | Odds ratio | | ? | ? | ? | ? | ? | ? |
| **Cefazolin**<br>J01DB04 | S | 20 | 13 | 0 | 0 | 0 | 13 | 0 |
| | R | 50 | 4 | 44 | 0 | 0 | 2 | 41 |
| | Coverage | 29% | 76% | 0% | ? | ? | 87% | 0% |
| | Odds ratio | | 8.1 | 0.0 | ? | ? | 16.3 | 0.0 |
| **Cefuroxime**<br>J01DC02 | S | 412 | 412 | 0 | 0 | 0 | 407 | 0 |
| | R | 418 | 0 | 418 | 0 | 0 | 13 | 398 |
| | Coverage | 50% | 100% | 0% | ? | ? | 97% | 0% |
| | Odds ratio | | ∞ | 0.0 | ? | ? | 31.8 | 0.0 |

*Table 2.12: An example of the data on cross-susceptibility/resistance that can be obtained from an isolate database.*

The crossABG|HAI and crossABG|CAI compiled for Rambam each included 27 pathogen groups and 55 * 55 pairs of antimicrobials with an entry for respectively cross-susceptibility and cross-resistance, respectively. This gave a total number of 27*55*55*2 = 163,650 entries in each crossABG. As it can be seen in the data example in Table 2.12, some of the antimicrobials and antimicrobial combinations,

did not have any AST results ("0"), and thereby the probability of cross-susceptibility/resistance could not be calculated ("?").

By using the Rambam AST statistics on antimicrobials tested more than 10 times, we could fill in 5241 (3.2%) of the entries in the crossABG|HAI and 5534 (3.4%) of the entries in the crossABG|CAI.

EUCAST has designed a set of interpretative rules to assist clinical microbiologists in the interpretation of antimicrobial susceptibility testing. Some of the rules are simple, for example: "IF S. aureus is resistant to oxacillin or cefoxitin, THEN report as resistant to all β-lactams" and some of the rules are complicated, for example: "IF Enterobacteriaceae are intermediate to tobramycin, resistant to gentamicin, and susceptible to amikacin, THEN report as resistant to tobramycin" (Leclercq et al., 2013). The simple rules could be integrated directly in a crossABGs, where for example the probability of *S. aureus* being susceptibility to cefuroxime, given resistance to oxacillin is 0% (OR=0) and likewise for the rest of the group of β-lactam antimicrobials. The more complicated rules could not be transferred to the crossABGs. The EUCAST expert rules represent an improvement in the reporting of susceptibility results, but covered only 265 (0.16%) of the entries in the Rambam crossABGs.

# CHAPTER 3. INTERPRETATIVE READING OF AST RESULTS

*This chapter describes the work done to develop and validate a mathematical method for interpretative reading of AST results, where probabilities of susceptibility to untested antimicrobials can be calculated. The resulting method generates ABG|ASTs, by adjusting the ABG to patient specific AST results. The content of this chapter is based primarily on Paper I* (Andreassen et al., 2015). *Figure 3.1 shows the relation between the content of this chapter and the rest of the thesis.*

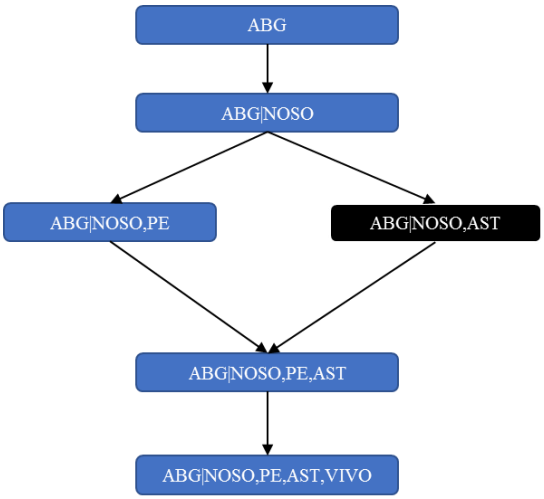


*Figure 3.1: This chapter describes the method developed to generate ABG|NOSO,AST.*

## 3.1. INTRODUCTION

From a Bayesian perspective, the instABG represents our prior evidence; the prior probability of susceptibility to antimicrobials. When AST results become available, they add more evidence to our knowledge about the susceptibility. In Paper I, we explored methods of interpretative reading of AST results. We used data from an isolate database containing 3,347 isolates with AST results, compiled between 2002 and 2004 at Rabin Medical Center in Israel. The examples and results in this chapter are based on this database and the corresponding instABG and crossABG.

From the crossABG (described in section 2.5), we can read the probability of susceptibility to an antimicrobial, given an AST result for one other antimicrobial. When we have multiple AST results that may affect the susceptibility to an untested antimicrobial, it becomes more complicated to calculate the combined effect. For an isolate with 21 AST results, the straightforward solution would to compile the 20-dimensional probability matrix for cefuroxime, conditional on the other 20 AST results. Bayes theorem can then be used directly to calculate the posterior probability of susceptibility to cefuroxime. This is far from a viable solution, because it would be impossible to populate the $2^{20}$ elements in this matrix even with an isolate database compiled over many years in a large hospital.
The aim was to develop and validate a practical method for interpretative reading of AST results where the susceptibilities are calculated from an instABG and a crossABG.

## 3.2. CALCULATING POSTERIOR SUSCEPTIBILITIES

To handle the combined effect of multiple AST results, we explored several versions of naïve and semi-naïve Bayesian methods, to calculate the probability of susceptibility to antimicrobials. The naïve Bayes approach includes all significant ORs for cross-resistance/susceptibility and assumes mutual independence. In the semi-naïve Bayesian methods, only a limited number of the most significant ORs were used.
Table 3.1 shows a segment of the crossABG for *E. coli* with OR for susceptibility to cefuroxime (cefur), given an AST result for another antimicrobial "A". The relevant ORs are bold, for example for ampicillin (A=ampi) with AST=R, we have $OR_{cefur|\neg ampi} = 0.63$.

| | Antimicrobial A | AST result | Cefuroxime | |
|---|---|---|---|---|
| | | | $OR_{cefur\|A}$ $p \leq 0.1$ | $OR_{cefur\|\neg A}$ $p \leq 0.1$ |
| Penicillin | Penicillin | | | |
| | Ampicillin | R | 23 | **0.63** |
| | Ampicillin-Sulbactam | | 6.9 | 0.40 |
| | Amoxicillin-Clavulanate | R | 5.1 | **0.30** |
| | Piperacillin | R | 4.5 | **0.59** |
| | Piperacillin/ Tazobactam | S | **1.6** | 0.11 |
| | Methicillin | | | |
| Cephalosporin | Cephalothin | R | ∞ | **0.60** |
| | Cefuroxime | S | ∞ | 0 |
| | Ceftazidime | S | **3.4** | 0.00 |
| | Ceftriaxone | S | **4.5** | 0 |
| | Cefepime | S | **2.9** | 0 |
| Carbapenem | Ertapenem | | NS | NS |
| | Imipenem | S | NS | NS |
| | Meropenem | S | NS | NS |
| Monobactam | Aztreonam | S | **3.4** | 0.01 |
| Glycopeptide | Vancomycin | | | |
| Macrolide | Erythromycin | | | |
| Tetracycline | Minocycline | S | **2.2** | 0.55 |
| | Tetracycline | S | **2.4** | 0.63 |
| Aminoglycoside | Amikacin | S | **1.8** | 0.09 |
| | Gentamicin | S | **2.0** | 0.14 |
| | Tobramycin | S | **3.7** | 0.10 |
| Quinolone | Ciprofloxacin | S | **5.0** | 0.18 |
| | Ofloxacin | S | **5.0** | 0.16 |
| Other | Chloramphenicol | | | |
| | Clindamycin | | | |
| | Colistin | S | NS | NS |
| | Fusidic acid | | | |
| | Rifampicin | | | |
| | Sulfa-Trim | S | **2.0** | 0.52 |

*Table 3.1: ORs for E. coli being susceptible to cefuroxime given susceptibility test results to other antimicrobials. NS: Odds ratio Not Significant. Blank field: Susceptibility to this antimicrobial not tested. S=susceptible and R=resistant.*

Table 3.2 shows an example of predicted susceptibilities with a naïve Bayesian method (Naïve) and a semi-naïve Bayesian method (min1max1). We only included ORs for cross resistance/susceptibility which were significantly different from 1. The limit of significance was arbitrarily chosen for the example in Table 3.2 as $p < 0.1$. The semi-naïve Bayesian method, denoted min1max1 method only included the largest of the ORs for antimicrobials to which the isolate was tested susceptible and the smallest of the ORs amongst those tested resistant. The same principle was used for a min2max2 method that included the two largest and the two smallest ORs.

| Antimicrobial class | Antimicrobial | AST result | Probability of susceptibility (%) | | |
|---|---|---|---|---|---|
| | | | instABG | Naïve | min1max1 |
| Penicillins | Penicillin | | | | |
| | Ampicillin | R | 31 | 0 | 0 |
| | Ampicillin-sulbactam | | 53 | | |
| | Amoxicillin-clavulanate | R | 64 | 99 | 57 |
| | Piperacillin | R | 41 | 47 | 11 |
| | Piperacillin-tazobactam | S | 89 | 100 | 88 |
| | Methicillin | | | | |
| Cephalosporins | Cephalothin | R | 33 | 30 | 9 |
| | Cefuroxime | S | 83 | 100 | 88 |
| | Ceftazidime | S | 91 | 100 | 99 |
| | Ceftriaxone | S | 86 | 100 | 100 |
| | Cefepime | S | 90 | 100 | 100 |
| Carbapenems | Ertapenem | | 100.0 | | |
| | Imipenem | S | 99.8 | | |
| | Meropenem | S | 99.3 | | |
| Monobactams | Aztreonam | S | 86 | 100 | 98 |
| Glycopeptides | Vancomycin | | | | |
| Macrolides | Erythromycin | | | | |
| Tetracyclines | Minocycline | S | 54 | 94 | 87 |
| | Tetracycline | S | 45 | 83 | 65 |
| Aminoglycosides | Amikacin | S | 89 | 100 | 94 |
| | Gentamicin | S | 84 | 100 | 92 |
| | Tobramycin | S | 81 | 100 | 89 |
| Quinolones | Ciprofloxacin | S | 73 | 100 | 98 |
| | Ofloxacin | S | 74 | 100 | 100 |
| Other | Chloram-phenicol | | | | |
| | Clindamycin | | | | |
| | Colistin | S | 98.9 | | |
| | Fusidic acid | | | | |
| | Rifampicin | | | | |
| | Sulfa-Trim | S | 59 | 87 | 61 |

*Table 3.2: Calculated susceptibilities to E. coli with a naïve Bayesian method ("Naïve") and a semi-naïve Bayesian method ("min1max1")*

## 3.3. VALIDATION OF THE EXPLORED METHODS

### 3.3.1. COMPARING NAÏVE AND SEMI-NAÏVE BAYESIAN METHODS

Table 3.3 shows the results of using several versions of naïve and semi-naïve Bayesian methods. The methods are named after the number of ORs used to calculate posterior probabilities of susceptibility. For example, the min0max3 method includes zero ORs on cross-resistance and the three highest significant ORs on cross-susceptibility (if they exist). The methods were validated by using a 5-fold cross validation, where each time one of the five sets was designated as the validation set, with the remaining four forming the learning set. The instABGs and crossABGs compiled from the learning set were used to calculate posterior probabilities in the validation set. We removed the AST results one at a time and used the different methods to calculate the given susceptibility. Then the normalised Brier distance(Brier, 1950) between the AST result and the calculated susceptibility was used to measure the quality of the calculated susceptibility. Table 3.3 shows the square root of the mean Brier distance of the estimated susceptibilities for the five validations sets, and the range the sets varied across.

| Number of ORs | Method | Norm. Brier Distance (%) | Range for the 5 validation sets |
|---|---|---|---|
| 0 | instABG | 37.7 | 37.3 - 38.4 |
| 1 | min0max1 | 35.3 | 34.8 - 35.6 |
| | min1max0 | 36.7 | 36.1 - 37.5 |
| 2 | min0max2 | 37.2 | 37.1 - 37.4 |
| | min1max1 | 25.6 | 25.3 - 26.0 |
| | min2max0 | 40.2 | 39.5 - 40.8 |
| 3 | min0max3 | 38.2 | 38.0 - 38.4 |
| | min1max2 | 26.0 | 25.7 - 26.1 |
| | min2max1 | 26.7 | 26.2 - 27.2 |
| | min3max0 | 42.1 | 41.3 - 42.9 |
| 4 | min0max4 | 38.6 | 38.4 - 38.9 |
| | min1max3 | 27.0 | 26.6 - 27.3 |
| | min2max2 | 25.3 | 24.8 - 25.6 |
| | min3max1 | 28.5 | 28.1 - 28.9 |
| | min4max0 | 43.0 | 42.3 - 43.9 |
| 6 | min3max3 | 26.0 | 25.7 - 26.4 |
| 8 | min4max4 | 26.7 | 26.4 - 27.1 |
| All | naïve | 28.2 | 27.8 - 28.5 |

*Table 3.3: Normalised Brier distances for calculated susceptibilities by using different Bayesian approaches.*

The normalised Brier distance between the instABG probabilities and the AST results for all isolates in the database was 37.7%. By generating patient specific ABG|ASTs with the naïve Bayes method we reduced the distance to 28.2%. We achieved the smallest distance of 25.3% with ABG|ASTs calculated by using the semi-naïve min2max2 method.

The Brier distances from the 5-fold validation were significantly smaller ($p<10^{-99}$, paired 2-tailed t-test) for the min2max2 method than for the instABG. The distance for the min2max2 was also significantly smaller than the distance for the min1max1 method ($p<10^{-9}$). The naïve Bayes approach is known to produce overconfident results, i.e. results too close to 0% or 100%, if the underlying assumption of independence is not well met. The naïve Bayes results in Table 3.3 indicates that this is the case, and this is most likely the reason that the semi-naïve methods perform better than the naïve method.

### 3.3.2. PERFORMANCE ON DIFFERENT PATHOGEN GROUPS

Figure 3.2 shows the performance of the min2max2 method on each pathogen group compared to the prior susceptibilities from the instABG. The presented normalised Brier distances for each pathogen group were averaged over the five validation sets. The normalised Brier distance was reduced with 13.3% for GN bacteria, 12.0% for Staphylococcus spp. and 3.5% for the rest of the GP bacteria on average. This indicates a better performance on GN isolates compared to GP isolates. This is could be related to a higher fraction of the cross-ABG being filled for GN bacteria, i.e. a higher fraction of significant cross-resistances and cross-susceptibilities.

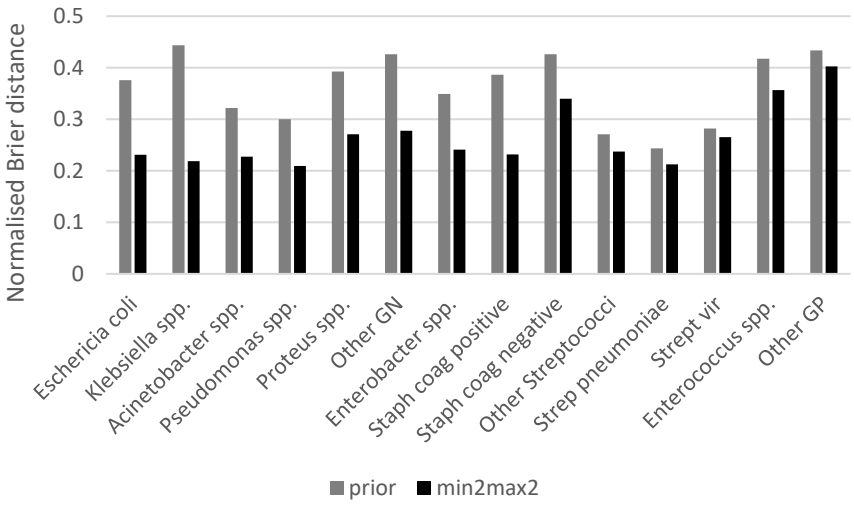


*Figure 3.2: Normalised Brier distances for each pathogen group averaged over 5 validation sets when using prior susceptibilities and the min2max2 method, respectively.*

### 3.3.3. PERFORMANCE WITH DIFFERENT P-VALUES

The results were generated with ORs for-cross resistance/susceptibility with the limit of significance $p < 0.1$. We explored how the limit of significance influenced the results. The results for different p values, ranging from 0.02 to 0.5 are illustrated on Figure 3.3, for respectively the prior susceptibilities from the instABG, the naïve Bayes method, and the min2max2 method.

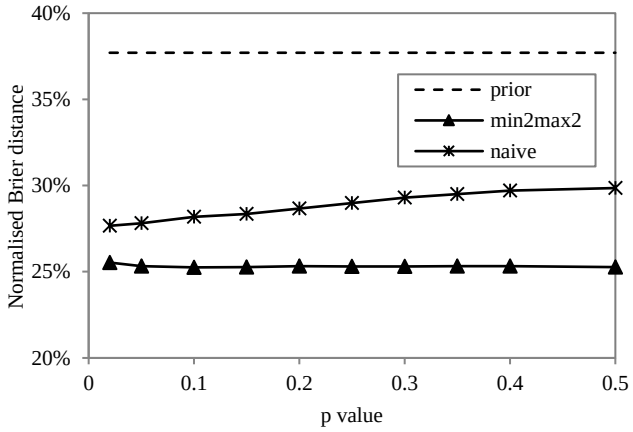


*Figure 3.3: Normalised Brier distances averaged over the five validation sets when using respectively the prior susceptibilities from the instABG, the naïve Bayes method, and the min2max2 method to calculate patient specific probabilities of susceptibility. The results were generated with different p values, ranging from 0.02 to 0.5.*

It can be seen from Figure 3.3 that irrespective of p value, the naïve Bayes method had lower normalised Brier distance than the prior probabilities and that the min2max2 method had lower normalised Brier distances than the naïve Bayes method. The decrease of the normalised Brier distance of the min2max2 method with the p value could be seen as an argument for using a high p value. This should however be balanced against the risk of obtaining "strange" estimates due to spurious ORs derived from very few susceptibility results. Since the reduction in normalised Brier distance was very small for p values above 0.1, $p = 0.1$ may be an appropriate choice.

## 3.4. DISCUSSION AND CONCLUSION

In conclusion, we achieved significantly more accurate predictions of microbial *in vitro* susceptibility to antimicrobials, than the prior probabilities stored in the instABG. The developed method is limited by being an approximate method. However, an exact Bayesian approach would require multidimensional conditional probability matrices, which is far beyond reach. The one-dimensional conditional probabilities in the crossABG represents a practical upper limit. It may therefore be considered a virtue, that useful posterior probabilities can be calculated from the limited information compiled from the isolate database.

The method was implemented in TREAT Steward. When possible the system used the min2max2 method, except when less than two ORs were available for cross-susceptibility and cross-resistance, respectively, in which case min1max1 was used. The implementation will be presented in Chapter 7.

# CHAPTER 4. THE EFFECT OF PRIOR ANTIMICROBIAL EXPOSURE

*This chapter describes the work done to quantify the effect of prior antimicrobial exposure at patient level. A quantification of increased resistance associated with prior antimicrobial exposure is a necessary step to be able to generate an ABG|PE for patients previously exposed to antimicrobials. The content of the chapter is based primarily on Paper II* (Sanden et al., 2016). *Figure 4.1 shows the relation between the content of this chapter and the rest of the thesis.*

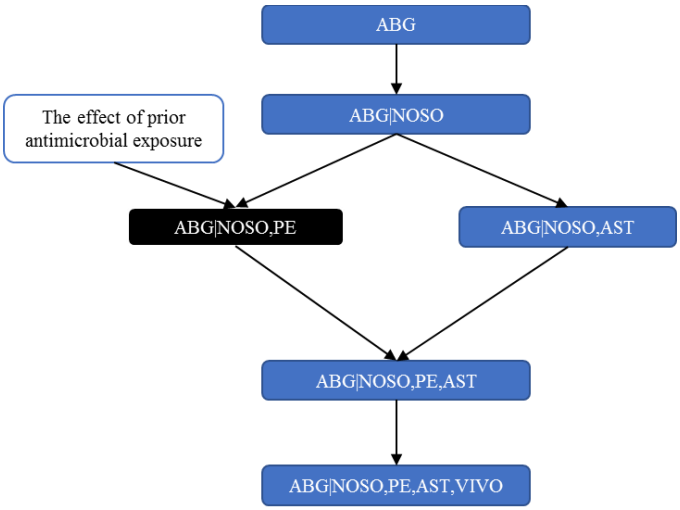


*Figure 4.1: This chapter describes the work done to quantify the effect of PE with the purpose of being able to generate an ABG|NOSO,PE.*

## 4.1. INTRODUCTION AND METHOD

The aim of the research published in Paper II was to quantify the association between recent antimicrobial exposure at patient level and subsequent antimicrobial resistance. Data were obtained from a series of prospective cohort studies carried out at Rabin Medical Center, Beilinson Hospital in Israel in the period from 2002-2011, where 4,232 patients suspected of infection were included. We analysed resistance to antimicrobials in bacterial isolates from patients with clinically significant and

microbiologically documented infections, starting antimicrobial treatment after obtaining cultures (n=775). Further details on the inclusion criteria are available in Paper II (Sanden et al., 2016).

Separate analyses were made for Gram negative (GN) and Gram positive (GP) bacterial isolates. The increase in bacterial resistance is expressed by ORs and 95% Confidence Intervals (CI) (Sanden et al., 2016). We calculated increased resistance to both single antimicrobials and to the following classes of antimicrobials:

- Tetracyclines
- Penicillins
- Penicillins combined with β-lactamase inhibitor (BLI)
- Cephalosporins
- Aminoglycosides
- Carbapenems
- Quinolones

The increase in resistance was calculated after the following types of exposure were analysed:

- Exposure to any antimicrobial class
- Exposure to the same antimicrobial class
- Exposure to other antimicrobial classes

## 4.2. RESISTANCE IN GN BACTERIA TO SINGLE ANTIMICROBIALS

Figure 4.2 illustrates the ORs for increased resistance in GN bacterial isolates from patients exposed to any antimicrobial compared to those with no exposure. The effect of exposure to any class ranged from an insignificant OR of 1.03 for chloramphenicol to a significant OR of 9.84 for imipenem-cilastatin.

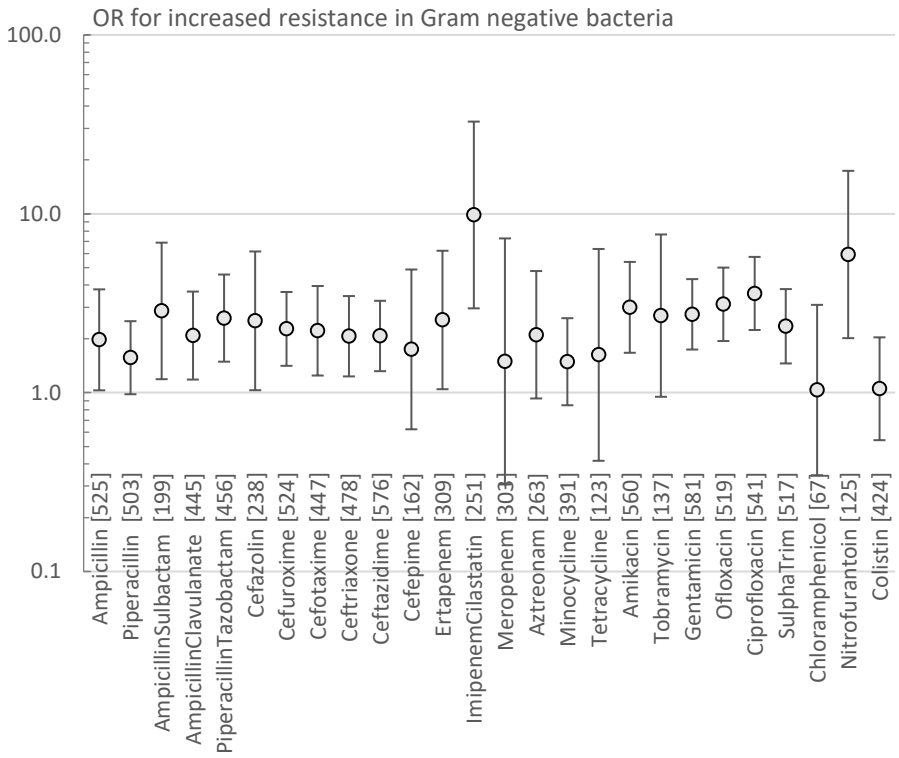


*Figure 4.2: OR for increased resistance in Gram negative bacteria from patients exposed to any antimicrobial compared to unexposed. Each antimicrobial is presented with number of AST results [in brackets]. Vertical bars indicate 95% confidence limits.*

Looking at resistance to antimicrobials within the same class, the prior exposure had almost the same effect on all antimicrobials within the same class. The only significant exception was amongst the carbapenems, where previous exposure to any class of antimicrobials had a greater effect on resistance to imipenem-cilastatin (OR=9.8) than to ertapenem (OR=2.6) or meropenem (OR=1.5).

GN bacteria from patients exposed to the same antimicrobial class as the tested antimicrobial, only showed significant ORs for quinolones, with an OR of 7.15 for ofloxacin and an OR of 5.11 for ciprofloxacin. The data for this analysis were sparse, since patients were seldom treated with the same antimicrobial twice within a month.

Looking at exposure to an antimicrobial from another class, the majority of the antimicrobials with significantly higher resistance when exposed to any class also had significant ORs after exposure to another class of antimicrobials. This indicates

an effect of cross-resistance between antimicrobial classes. The highest OR for increased resistance after exposure to an antimicrobial from another class was for nitrofurantoin with OR 5.92 (2.02-17.38). Table 4.1 shows the analysis for the three most common prior antimicrobial treatments of patients with current infection with GN bacteria. Data details for all the 26 included antimicrobials are available in Paper II (Appendix II) (Sanden et al., 2016). For example, for ceftriaxone (cftax) the probability of resistance goes from being 27% for no exposure to 44% for patient previously exposed to any antimicrobial within the last month, resulting in a OR of 2.1(1.2-3.5). After exposure to a cephalosporin (same class), resistance to cftax increased with an OR of 2.3 (0.8–7.0) and after exposure to another class, resistance to cftax increased with an OR of 3.1 (1.8–5.3). In general resistance was increased most by exposure to the same class following by exposure to any class and other class.

| **Tested antimicrobial** | **Type of prior antimicrobial exposure** | | | | | | |
|---|---|---|---|---|---|---|---|
| | None | Any class | | Same class | | Other class | |
| | Res | Res | OR (95% CI) | Res | OR (95% CI) | Res | OR (95% CI) |
| Ampicillin-clavulanate | 41 % | 60 % | 2.1 (1.2-3.7) | 73 % | 3.8 (1.0–4.4) | 57 % | 1.8 (1.0–3.4) |
| **Ceftriaxone** | 27 % | 44 % | 2.1 (1.2–3.5) | 46 % | 2.3 (0.8–7.0) | 42 % | 1.9 (1.1–3.4) |
| **Ciprofloxacin** | 30 % | 61 % | 3.6 (2.2–5.7) | 69 % | 5.1 (1.7–15.0) | 57 % | 3.1 (1.8–5.3) |

*Table 4.1: Resistance to the three most common prior antimicrobial treatments of patients with infected with GN bacteria. (Res = Probability of resistance)*

## 4.3. RESISTANCE IN GP BACTERIA TO SINGLE ANTIMICROBIALS

The results of the analysis of resistance in GP are illustrated on Figure 4.3. The number of AST results was considerably lower for GP bacteria than for GN bacteria, and the results did not show any significant increase in resistance after exposure to antimicrobials.

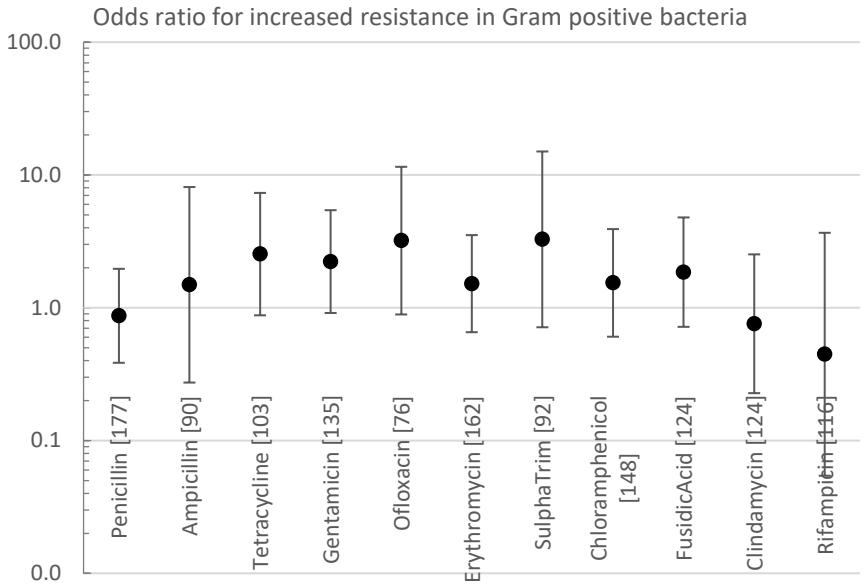


*Figure 4.3: OR for increased resistance in GP bacteria from patients exposed to any antimicrobial compared to unexposed. Each antimicrobial is presented with number of AST results [in brackets]. Vertical bars indicate 95% confidence limits.*

## 4.4. RESISTANCE IN GN BACTERIA TO CLASSES OF ANTIMICROBIALS

For seven classes of antimicrobials, Figure 4.4 illustrates the ORs for increased resistance in bacterial isolates from patients exposed to any antimicrobial compared to those with no exposure. Across the antimicrobial classes, the results indicated a ranking of antimicrobials with quinolones and carbapenems being most effected by prior antimicrobial exposure, followed by aminoglycosides, penicillins+BLI, and cephalosporins.

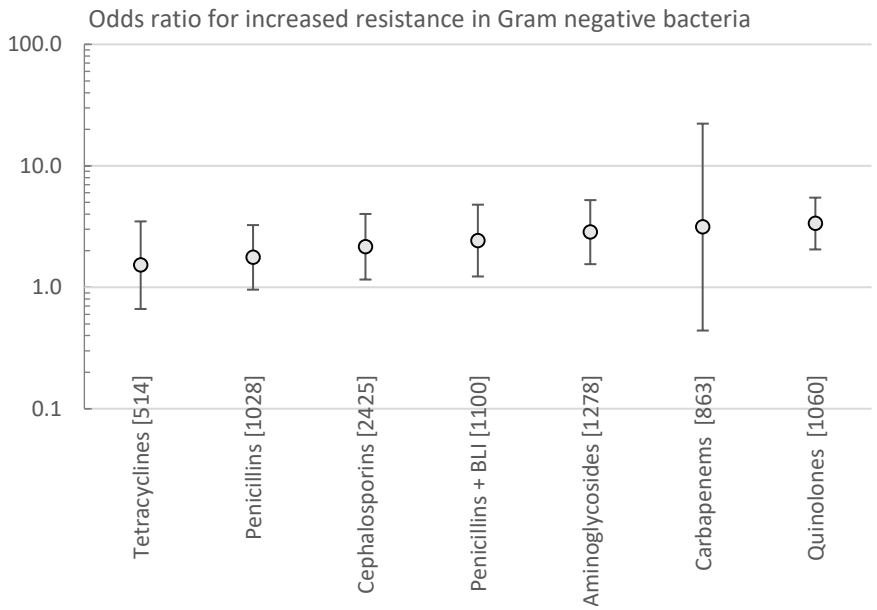


*Figure 4.4: OR for increased resistance in GN bacteria to antimicrobial classes, when analysing isolates from patients exposed to any antimicrobial. Each antimicrobial class is presented with number of AST results [in brackets]. Vertical bars indicate 95% confidence limits.*

## 4.5. DISCUSSION AND CONCLUSION

In conclusion, we were able to quantify the association between antimicrobial exposure and subsequent resistance at the level of the individual treated. Our results showed that an increase in resistance after exposure to antimicrobials was driven by both exposure to the same class, as well as by cross-resistance after exposure to other antimicrobial classes. However, to be fully applicable in clinical use, the analysis should be expanded to give pathogen- and antimicrobial-specific results. These expansions would require a substantially larger dataset.

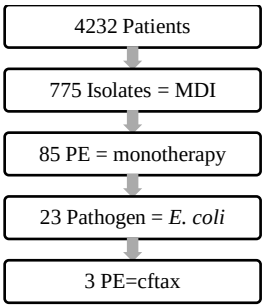


*Figure 4.5: The selection of data on prior exposure for a specific pathogen (E. coli) and a specific antimicrobial (cftax).*

Our study included 4,232 patients with 775 clinically significant isolates, (Figure 4.5). As illustrated on Figure 4.5, 85 of these isolates were from patients with PE to a single antimicrobial. When analysing a specific pathogen, for example *E. coli*, we were left with 23 isolates and the most common PE, cftax, were only associated with 3 of these isolates. Even through the study included more than 4000 patients, this was far from being enough data to generate pathogen- and antimicrobial specific results with convincing statistical power, and it would be logistically difficult to collect enough data.

Our results on exposure to any, same and other antimicrobials do however indicate a need to modify the expected coverage of empirical antimicrobial treatments for patients recently exposed to antimicrobials. This was a motivation for exploring another approach to modify the ABG|HAI or ABG|CAI for patients previously exposed to antimicrobials, which will be addressed in Chapter 5.

# CHAPTER 5. MODIFYING THE ABG TO ACCOUNT FOR PE

*This chapter describes a mathematical method (patent pending) developed to modify either the ABG|CAI or the ABG|HAI with respect to a patient's prior antimicrobial exposure. This chapter serves as an operationalisation of Paper II (described in Chapter 4). The method will be described by giving a patient example, and the generalised mathematics is described in Appendix A. Figure 5.1 shows the relation between the content of this chapter and the rest of the thesis.*

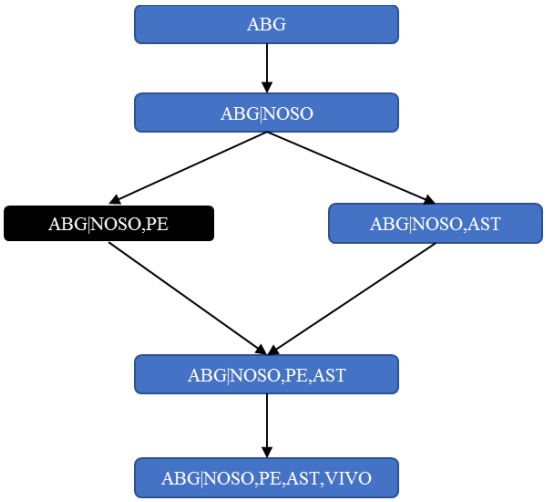


*Figure 5.1: This chapter describes the method used to generate ABG|NOSO,PE.*

## 5.1. THE SUSCEPTIBILITY TO AN ANTIMICROBIAL AFTER PE TO THE SAME ANTIMICROBIAL CLASS

To modify the susceptibility to an antimicrobial, given PE to that antimicrobial, we need the corresponding OR for increased resistance. In the study (Sanden et al., 2016), described in Chapter 4, we observed that PE had almost the same effect on all antimicrobials within the same class. From Paper II (Sanden et al., 2016) we have ORs for increased resistance to antimicrobial classes in GN bacteria (Table 5.1). The ORs are associated with PE to any, same, and other class of antimicrobial, respectively.

| GN bacteria | PE=any class | | PE=same class | | PE=other class | |
|---|---|---|---|---|---|---|
| **Tested antimicrobial class** | **N** | **$OR_{class}$ (95% CI)** | **N** | **$OR_{class}$ (95% CI)** | **N** | **$OR_{class}$ (95% CI)** |
| Tetracyclines | 514 | 1.52 (0.66-3.49) | <10 | | 512 | 1.45 (0.63-3.35) |
| Penicillins | 1028 | 1.76 (0.96-3.25) | <10 | | 1012 | 1.75 (0.95-3.23) |
| Cephalosporins | 2425 | 2.16 (1.16-4.01) | 2110 | 1.52 (0.37-6.29) | 2339 | 2.10 (1.05-4.21) |
| Penicillins + BLI | 1100 | 2.42 (1.23-4.79) | 960 | 2.55 (0.59-11.03) | 1064 | 2.36 (1.04-5.33) |
| Aminoglycosides | 1278 | 2.84 (1.55-5.22) | <10 | | 1262 | 2.46 (1.30-4.64) |
| Carbapenems | 863 | 3.13 (0.44-22.25) | <10 | | 848 | 1.77 (0.21-14.88) |
| Quinolones | 1060 | 3.35 (2.05-5.47) | 917 | 6.02 (1.90-19.12) | 1004 | 2.67 (1.43-4.98) |

*Table 5.1: ORs for increased resistance in GN bacteria associated with exposure to respectively any, same, and other class of antimicrobial (Sanden et al., 2016).*

It was difficult to generate significant ORs for increased resistance, given exposure to the same class. This was probably due to the limited number of patients with PE and corresponding AST result on the same class of antimicrobials. However, for a given antimicrobial "A", $OR_{\neg a|PE=same}$ could be expected to higher or at least equal to $OR_{\neg a|PE=any}$. Where $OR_{\neg a|PE=same}$ describes the change in resistance towards antimicrobial A, given PE to an antimicrobial of the same class, and $OR_{\neg a|PE=same}$, describes the change in resistance towards A, given exposure to any type of antimicrobial. In the following we will use $OR_{\neg a|PE=any}$ to modify the susceptibility to previously given antimicrobials. This means that we, for example, assume conservatively for cephalosporins that $OR_{\neg ceph|PE=same} = 2.16$.

Consider as an example, a patient suspected of being infected with a community-acquired *E. coli* infection. For this patient, the ABG|CAI (described in Chapter 2, section 2.3) can be used for guidance on empirical treatment. A small segment of the 55 antimicrobials in the Rambam ABG|CAI for *E. coli* is shown Table 5.2.

| **Antimicrobial** | Amoxicillin-clavulanate | Piperacillin-tazobactam | Cefazolin | Cefuroxime | Ceftriaxone |
|---|---|---|---|---|---|
| **ABG\|CAI** | 80% | 94% | 50% | 71% | 75% |
| **PE** | | | | | X |
| **ABG\|CAI,PE** | P*(amoCl) | P*(pipTa) | P*(cefa) | P*(cefur) | P*(cftax) |

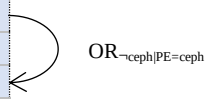


*Table 5.2: A segment of the ABG|CAI from Rambam, listing the susceptibility of E. coli. The patient specific susceptibility after PE to ceftriaxone will be shown in the ABG|CAI,PE.*

If the medical history for this patient includes recent antimicrobial treatment, then the probability of resistance to antimicrobials could be expected to increase (Bell et al., 2014; Costelloe et al., 2010; Sanden et al., 2016), as demonstrated in Chapter 4. The susceptibilities in the ABG|CAI, should then be modified with respect to the effect of the patients PE. The resulting probabilities is the represented in an ABG|CAI,PE. Consider as an example, a patient with PE=cftax. The prior probability of susceptibility to cftax, can be read from the ABG|CAI to be P(cftax)=75% (Table 5.2). By modifying P(cftax) with the OR for increased resistance to a cephalosporin given PE to a cephalosporin, denoted $OR_{\neg ceph|PE=ceph}$, we get P*(cftax).

In the following we will calculate P*(cftax). The probability of resistance to cftax, is denoted P(¬cftax), where P(cftax)=1-P(¬cftax). First, the prior odds $OD_{cftax}$ for susceptibility to cftax is calculated from the prior probability of susceptibility, P(cftax), as:

$$OD_{\text{cftax}} = \frac{P(\text{cftax})}{P(\neg\text{cftax})} = \frac{0.75}{1-0.75} = 3$$

The prior odds are then modified with $OR_{\neg ceph|PE=ceph}$=2.16. The posterior odds for susceptibility to cftax after exposure to cftax, is denoted $OD^*_{cftax}$. By using Eq. 4 and Eq. 10 from Appendix A, $OD^*_{cftax}$ can be calculated as:

$$OD^*_{cftax} = OD_{\text{cftax}} \cdot \frac{1}{OR_{\neg ceph|PE=ceph}} = 3 \cdot \frac{1}{2.16} = 1.40$$

The posterior probability of susceptibility, denoted P*(cftax), can then be calculated by using the mathematical relationship between odds and probability:

$$OD^*_{\text{cftax}} = \frac{P^*(cftax)}{P^*(\neg cftax)}$$

$$\Leftrightarrow$$

$$P^*(\text{cftax}) = \frac{OD^*_{\text{cftax}}}{1+ OD^*_{\text{cftax}}} = \frac{1.4}{1+1.4} = 0.58 = 58\%$$

This means that for the patient previously has been treated with cftax, then the probability of cftax being effective against an *E. coli* goes from being 75% to 58%, which makes the antimicrobial less attractive to use. We can now fill in the susceptibility to cftax in an ABG|CAI,PE, as shown in Table 5.3.

| **Antimicrobial** | Amoxicillin-clavulanate | Piperacillin-tazobactam | Cefazolin | Cefuroxime | Ceftriaxone |
|---|---|---|---|---|---|
| **ABG\|CAI** | 80% | 94% | 50% | 71% | 75% |
| **PE** | | | | | X |
| **ABG\|CAI, PE** | P*(amoCl) | P*(pipTa) | 34% | 53% | 58% |

$OR_{\neg ceph|PE=ceph}$

*Table 5.3: A segment of the ABG|CAI from Rambam, listing the susceptibility of E. coli. The ABG|CAI,PE, now includes the susceptibility of E. coli to ceftriaxone (PE) and the susceptibility to antimicrobials of the same class (cephalosporins)*

The susceptibilities to the other cephalosporins are likewise calculated by modifying the prior susceptibility from the ABG|CAI with $OR_{\neg ceph|PE=ceph}$.

## 5.2. THE SUSCEPTIBILITY TO AN ANTIMICROBIAL AFTER PE TO OTHER CLASSES OF ANTIMICROBIALS

The question is now, how to modify the susceptibilities to the antimicrobials from other classes in the ABG|CAI, PE. Our study, described in Chapter 4 (Sanden et al., 2016), showed increased resistance after exposure to antimicrobials from another class, and hence we would in our example also expect PE to cftax to affect the susceptibility to other antimicrobials. For the given example, we need for the OR for increased resistance to amoCl and to pipTa, given exposure to cftax. Unfortunately, no studies have to our knowledge been able to assess the increased resistance of a given pathogen after exposure to different antimicrobials. This was a motivation for

inventing a method that takes advantage of our knowledge on cross-resistance between antimicrobials.

The cross-resistance between cftax and the other antimicrobials from our example (in Table 5.3) are shown in the crossABG|CAI in Table 5.4. Here we can read that the probability of susceptibility to amoCl given resistance to cftax, P(amoCl|¬cftax)=39%. The change in susceptibility from P(amoCl)=80% to P(amoCl|¬cftax)=39% corresponds to an $OR_{amoCl|\neg cftax}$=0.16.

| **crossABG\|CAI** Pathogen: *E. coli* | | **Ceftriaxone** | |
|---|---|---|---|
| | | cftax | ¬cftax |
| **Amoxicillin-clavulanate** | P(amoCl\|CFTAX) | **91%** | **39%** |
| J01CR02 | $OR_{amoCl\|cftax}$ | 2.57 | **0.16** |
| **Piperacillin-tazobactam** | P(pipTa\|CFTAX) | 96% | 86% |
| J01CR05 | $OR_{pipTa\|cftax}$ | 1.53 | 0.42 |

*Table 5.4: The crossABG|CAI with cross-susceptibility/resistance between ceftriaxone/amoxicillin-clavulanate and ceftriaxone/piperacillin-tazobactam.*

As a consequence of the cross-resistance between cftax and amoCl, we modify the susceptibility to amoCl, given PE to cftax.

By using Eq. 8 from Appendix A, the probability of susceptibility to amoCl given PE to cftax can be calculated as:

$$P^*(amoCl) = P(amoCl|cftax) \cdot P^*(cftax) + P(amoCl|\neg cftax) \cdot P^*(\neg cftax)$$

From the crossABG|CAI (Table 5.4) we can read that:

- P(amoCl|cftax) = 0.91
- P(amoCl|¬cftax) = 0.39

From Table 5.3 we have

P*(cftax) = 58%, and P*(¬cftax) = 1- P*(cftax) =42%. By inserting these values, we get:

$$P^*(amoCl) = P(amoCl|cftax) \cdot P^*(cftax) + P(amoCl|\neg cftax) \cdot P^*(\neg cftax)$$

$$= 0.91 \cdot 0.58 + 0.39 \cdot 0.42 = 0.69 = 69\%$$

This means that for a patient previously treated with cftax, the probability of amoCl being effective against an *E. coli* infection goes from being 80% to 69%. We can now fill in the susceptibility to amoCl in the ABG|CAI, PE as shown in Table 5.5. The result of the similar calculation made for pipTa can also be seen in Table 5.5.

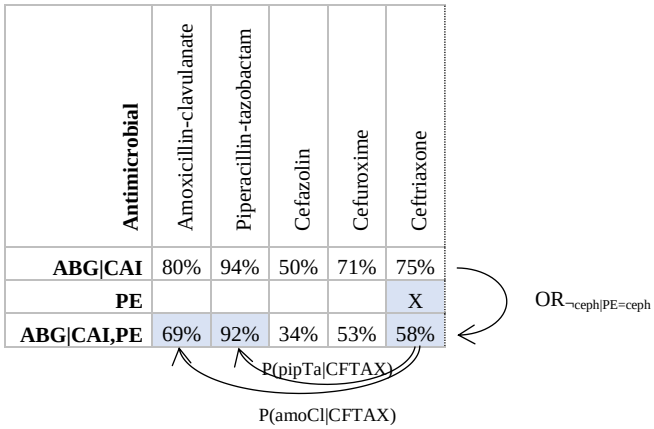


*Table 5.5: A segment of the ABG|CAI from Rambam, listing the susceptibility of E. coli. The ABG|CAI,PE, now includes the susceptibility of E. coli to ceftriaxone (PE) and the susceptibility to antimicrobials of the same class (cephalosporins) and the susceptibility to antimicrobials of another class (penicillins).*

# CHAPTER 6. MODIFYING THE ABG TO ACCOUNT FOR BOTH PE AND AST

*This chapter describes a mathematical method (patent pending) developed to modify either the ABG|CAI or the ABG|HAI with respect to both patient specific PE and AST results. Figure 6.1 shows the relation between the content of this chapter and the rest of the thesis.*

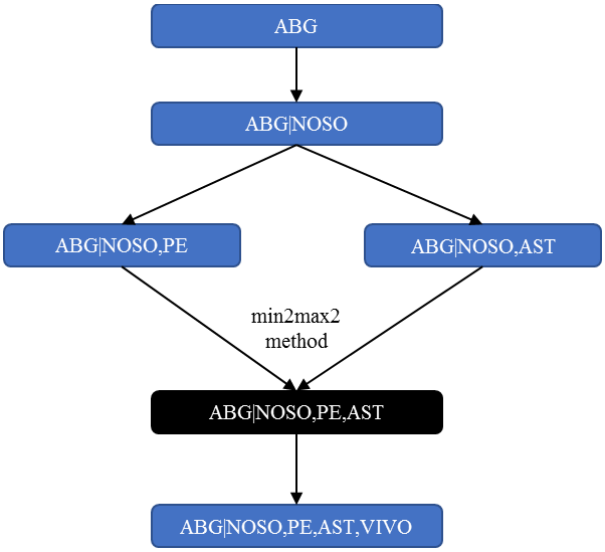


*Figure 6.1: This chapter describes the method used to generate ABG|NOSO,PE,AST.*

When AST results become available for patients previously exposed to antimicrobials these results should also be used to modify the susceptibility to untested antimicrobials (as described in Chapter 3). Now we need an patient specific ABG that accounts for both PE and AST results, denoted as ABG|CAI,PE,AST. Consider the situation, where an AST result is available, showing that *E. coli* is susceptible to cefuroxime (cefur). An ABG|CAI,PE,AST is added in Table 6.1, where the confirmed susceptibility to cefur is expressed as 100% probability of susceptibility.

| **Antimicrobial** | Amoxicillin-clavulanate | Piperacillin-tazobactam | Cefazolin | Cefuroxime | Ceftriaxone |
|---|---|---|---|---|---|
| **ABG\|CAI** | 80% | 94% | 50% | 71% | 75% |
| **PE** | | | | | X |
| **ABG\|CAI,PE** | 69% | 92% | 34% | 53% | 58% |
| **AST** | | | | S | |
| **ABG\|CAI,PE,AST** | ? | ? | ? | 100% | ? |

*Table 6.1: A segment of the Rambam ABG|CAI, listing susceptibilities for E. coli. The ABG|CAI,PE accounts for PE to ceftriaxone and the ABG|CAI,PE,AST, will account for both PE to ceftriaxone and for the AST result: cefuroxime=S.*

To express the effect of both PE=cftax and AST for cefur=S, we will use an OR for each factor affecting the susceptibility. Taking amoCl as example, the OR for susceptibility to amoCl, after exposure to cftax, is denoted $OR_{amoCl|PE=cftax}$, and is calculated as:

$$OR_{amoCl|PE=cftax} = \frac{OD^{*}_{amoCl}}{OD_{amoCl}} = \frac{P^{*}(amoCl)}{P^{*}(\neg amoCl)} \cdot \frac{P(\neg amoCl)}{P(amoCl)} = \frac{0.69}{0.31} \cdot \frac{0.20}{0.80} = 0.56$$

Where P(amoCl)=80% comes from the Rambam ABG|CAI and P*(amoCl)=69% comes from the ABG|CAI, PE (Table 6.1). From the crossABG|CAI we have the OR for susceptibility to amoCl given cefur=S, $OR_{amoCl|cefur}$=4.73 (Table 6.2).

| **CAI statistics**<br>Pathogen: *E. coli* | | | **Cefuroxime**<br>J01DC02 | |
|---|---|---|---|---|
| Antimicrobial | AST statistics | | S | R |
| **Amoxicillin-clavulanate**<br>J01CR02 | S | 4914 | 4058 | 532 |
| | R | 1226 | 214 | 827 |
| | Coverage | 80.0% | 95.0% | 39.1% |
| | Odds ratio | | **4.73** | 0.16 |

*Table 6.2: The crossABG|CAI for susceptibility/resistance between cefuroxime and amoxicillin-clavulanate.*

The next step was to combine the effect of PE and AST results. In Chapter 3 we took advantage of the semi-naïve Bayesian methods min1max1 and min2max2, to calculate the probability of susceptibility. These methods were also used to modify the ABG to multiple PE's and AST results. The methods use the largest available ORs for increased resistance and the smallest ORs for decreased resistance. In the given example, we use min1max1 to write:

$$OR^{*}_{amoCl} = OR_{amoCl|PE=cftax} \cdot OR_{amoCl|cefur} = 0.56 \cdot 4.73 = 2.63$$

By using Eq. 4 from Appendix A, we can calculate the odds of susceptibility to amoCl:

$$OD^{*}_{amoCl} = OR^{*}_{amoCl} \cdot OD_{amoCl} = 2.63 \cdot \frac{0.80}{0.20} = 10.52$$

Finally, the posterior probability of susceptibility to amoCl is calculated as:

$$P^{*}(amoCl) = \frac{OD'_{amoCl}}{1+OD'_{amoCl}} = \frac{10.52}{1+10.52} = 0.91 = 91\%$$

Thereby the probability of *in vitro* susceptibility to amoCl, given PE=cftax and cefur=S is 91%. The results of the similar calculations made for the other antimicrobials can be seen in Table 6.3.

| **Antimicrobial** | Amoxicillin-clavulanate | Piperacillin-tazobactam | Cefazolin | Cefuroxime | Ceftriaxone |
|---|---|---|---|---|---|
| **ABG\|CAI** | 80% | 94% | 50% | 71% | 75% |
| **PE** | | | | | X |
| **ABG\|CAI, PE** | 69% | 92% | 34% | 53% | 58% |
| **AST** | | | | S | |
| **ABG\|CAI, PE, AST** | 91% | 97% | 73% | 100% | 100% |

*Table 6.3: A segment of the Rambam ABG|CAI, listing susceptibilities for E. coli. The ABG|CAI,PE accounts for PE to ceftriaxone and the ABG|CAI,PE,AST, now accounts for both PE to ceftriaxone and for the AST result: cefuroxime=S.*

Table 6.4 shows an ABG|CAI,PE,AST were an *E. coli* isolate was tested resistant to cefur. It can be seen that the AST result for cefur affects the susceptibility both to the other cephalosporins and also to the penicillins. Due to cross-resistance between cefur and cefazolin the AST result cefur=R, results in 0% susceptibility to cefazolin. Cross-resistance between cefur and the penicillin amoCl gives a decrease in the susceptibility to amoCl from 69% to 27%. It can also be seen from Table 6.3 and Table 6.4 that the AST result for cefur, had a stronger effect on the other cephaloporins, than on the penicillins.

| **Antimicrobial** | Amoxicillin-clavulanate | Piperacillin-tazobactam | Cefazolin | Cefuroxime | Ceftriaxone |
|---|---|---|---|---|---|
| **ABG\|CAI** | 80% | 94% | 50% | 71% | 75% |
| **PE** | | | | | X |
| **ABG\|CAI, PE** | 69% | 92% | 34% | 53% | 58% |
| **AST** | | | | R | |
| **ABG\|CAI, PE, AST** | 27% | 81% | 0% | 0% | 3% |

*Table 6.4: A segment of the Rambam ABG|CAI, listing susceptibilities for E. coli. The ABG|CAI,PE accounts for PE to ceftriaxone and the ABG|CAI,PE,AST, now accounts for both PE to ceftriaxone and for the AST result: cefuroxime=R.*

This example included the susceptibility to five antimicrobials, but the principles for modifying the *in vitro* susceptibilities would be the same for the rest of the antimicrobials available at a given location.

# CHAPTER 7. IMPLEMENTING THE PERSONALISED ABG

*The developed in vitro susceptibility modifications were implemented in a software solution for antimicrobial stewardship (TREAT Steward). This chapter illustrates the implementation by going through a patient example.*

During the project, we focused on making the research operational, by developing practical applications, with the aim of shortening the way from research to an implemented solution available for clinicians and patients. Handling the patient specific factors that can affect the institutional ABG, can be a complicated task for the clinician, who must choose the most appropriate antimicrobial. A software-based application incorporating the expected effect of the patient specific factors could serve as decision support for clinicians, in the process of selecting the antimicrobial treatment.

## 7.1. TREAT STEWARD

The developed methods were implemented in a software solution for antimicrobial stewardship, TREAT Steward (TREAT), which has been shown to reduce inappropriate antimicrobial treatments at hospitals (Paul et al., 2006). TREAT uses Causal Probabilistic Network (CPN) technology. CPNs, also called Bayesian networks, can for example, represent the probabilistic relationships between diseases and symptoms. TREAT provides decision support by calculating the probability of infection, the most likely diagnosis and the responsible pathogen(s). From this, a cost-benefit analysis balances the benefits (survival) and costs (side-effects, resistance development, direct costs) of potential antimicrobial treatment regimens (TREATsystems.com, 2017).

Figure 7.1 and Figure 7.2 show the graphical user interface for the decision support feature in TREAT. Figure 7.1 shows a summary of the findings for a fictive patient example, a 71-year-old male with symptoms indicating pneumonia.

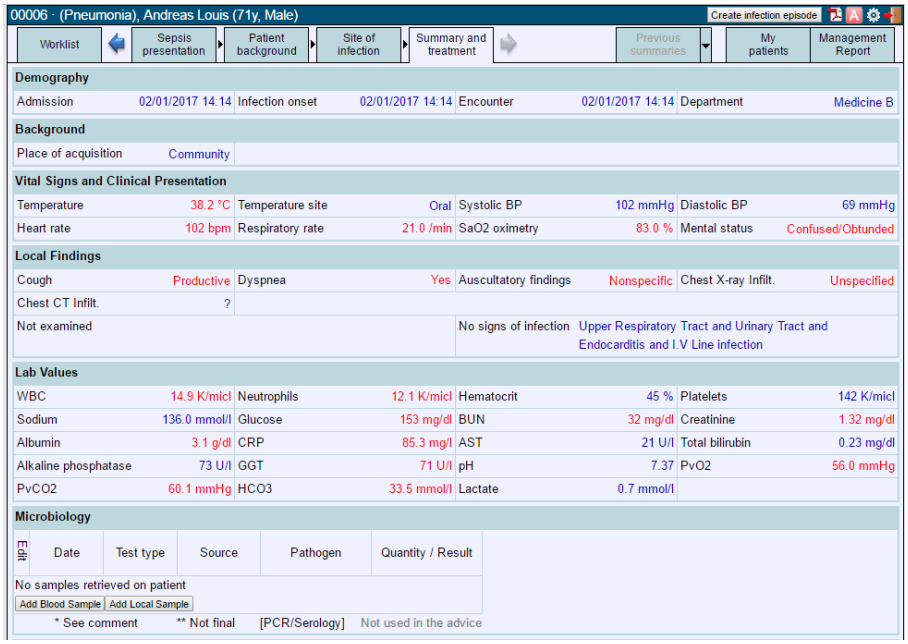


*Figure 7.1: The user interface of TREAT showing a summary of the findings for a fictive patient.*

Figure 7.2 shows the user interface of the decision support feature in TREAT, for the patient example in Figure 7.1. On the left side, the "TREAT diagnosis" suggests 100% probability of pneumonia. In the middle, the suggested pathogen distribution is shown and on the right side of Figure 7.2, the recommended antimicrobial treatments are shown; the top 1 treatment recommendation in this case being ampicillin. For each of the pathogens the probability of coverage by ampicillin is indicated by the blue portion of the bar, with red indicating not covered.

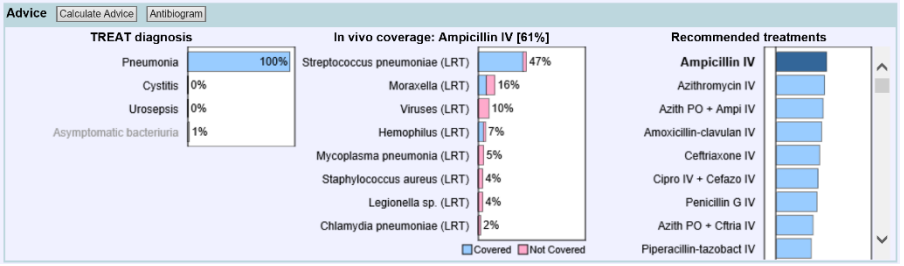


*Figure 7.2: The user interface of TREAT showing the decision support feature.*

The *in vivo* coverage of ampicillin across all pathogens in the suggested pathogen distribution is 61% (shown in heading above the pathogen distribution).

## 7.2. IMPLEMETATION IN TREAT STEWARD

The work presented in this thesis contributed to the TREAT system by providing methods to estimate personalised *in vitro* susceptibilities. The methods for *in vitro* susceptibility modifications were integrated with the *in vivo* susceptibility modifications already made by TREAT (Figure 7.3).

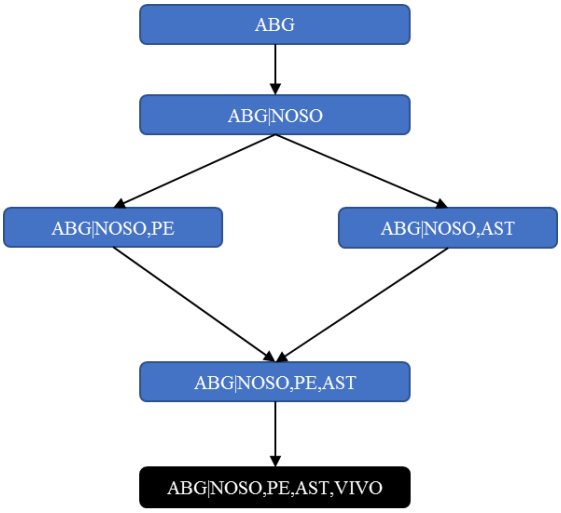


*Figure 7.3: By implementing the developed methods for in vitro susceptibility modifications in TREAT susceptibilities in vivo susceptibility modifications already made by TREAT.*

The *in vivo* modifications in TREAT are specified by the user for each infection site. This includes adjustments to the bioavailability and penetrance (e.g. of the blood-brain barrier) as well as adjustments for the effect of bacteriostatic versus bactericidal treatments.

## 7.3. PATIENT EXAMPLE

In the following the implementation of the personalised ABGs into the TREAT system will be illustrated by going through a patient example. Consider the patient example from section 7.1, where no PE or AST results are affecting the susceptibility. The probabilities of susceptibility are in this case solely based on the ABG|CAI. Table 7.1 shows a segment of the implemented ABG|CAI and Table 7.2 explains the color-codes used in the implemented ABGs.

| | Amoxicillin | Amoxicillin-clavula | Ampicillin | Azithromycin | Cefalexin | Cefazolin | Ceftazidime | Ceftriaxone |
|---|---|---|---|---|---|---|---|---|
| Acinetobacter sp. | 28.4% | 43.0% | 28.4% | - | - | - | 57.5% | 57.5% |
| Klebsiella sp. | - | 73.4% | - | - | 54.0% | 54.0% | 59.8% | 59.8% |
| Legionella sp. | - | - | - | 90.0% | - | - | - | - |
| Moraxella | 53.8% | 99.5% | 53.8% | 95.3% | - | - | 100.0% | 100.0% |
| Staphylococcus aureus | 10.0% | 40.0% | 10.0% | 66.5% | 67.9% | 67.9% | - | 60.0% |
| Staphylococcus coagulase negative | 52.9% | 63.2% | 52.9% | 46.4% | 49.5% | 49.5% | - | 90.0% |
| Enterococcus sp. | 92.4% | 92.0% | 92.4% | 20.2% | - | - | - | - |
| Streptococcus viridans | 86.2% | 79.6% | 86.2% | 79.2% | 79.6% | 79.6% | 94.1% | 94.1% |
| Streptococcus pneumoniae | 95.0% | 95.0% | 95.0% | 90.0% | 85.0% | 85.0% | 95.0% | 97.1% |
| Citrobacter sp. | - | 72.8% | - | - | 51.5% | 51.5% | 95.7% | 95.4% |
| E. coli | 26.6% | 80.0% | 26.6% | - | 53.2% | 53.2% | 74.8% | 74.9% |

*Table 7.1: A segment of an implemented ABG|CAI showing probability of in vitro susceptibility for different pathogen/antimicrobial combinations.*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0.0-4.9 | 5.0-14.9 | 15.0-24.9 | 25.0-34.9 | 35.0-44.9 | 45.0-54.9 | 55.0-64.9 | 65.0-74.9 | 75.0-84.9 | 85.0-94.9 | 95.0-100 |

*Table 7.2: The color-scale used to indicate the probability of susceptibility. Red indicates a low coverage, yellow indicates intermediate coverage, and green indicates high coverage.*

Figure 7.4 shows the advice given by TREAT, when no PE or AST results are entered for the patient. TREAT now provides the opportunity to enter PE ("Antibiotics last month"). In this example ceftriaxone is entered (Figure 7.5). The recalculated advice, which takes PE into account, can be seen on Figure 7.6.

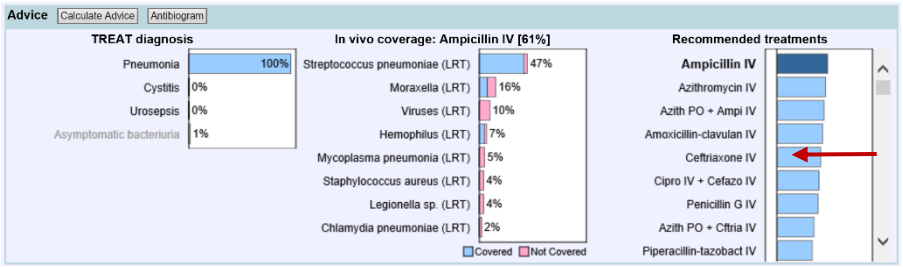


*Figure 7.4: The TREAT advice when no PE and no AST.*

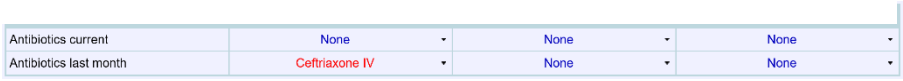


*Figure 7.5: Ceftriaxone is entered in as PE*

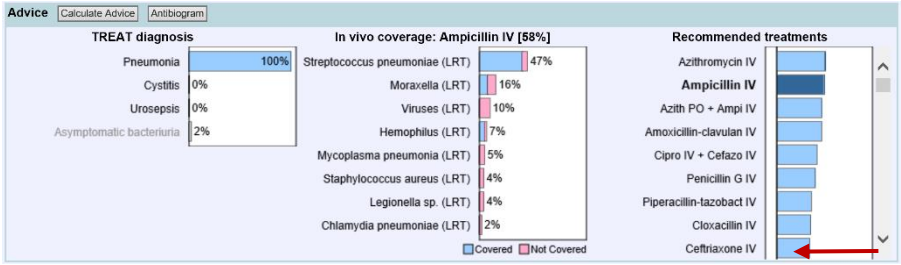


*Figure 7.6: The TREAT advice when PE=ceftriaxone and no AST.*

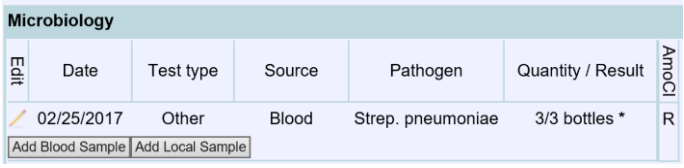


*Figure 7.7: The AST result is entered: strep. pneumoniae is tested resistant (R) to amoCl.*

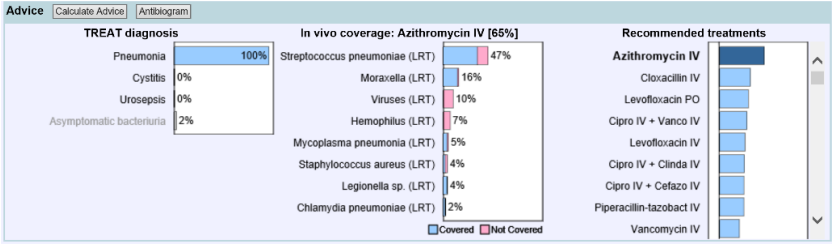


*Figure 7.8: The TREAT advice when PE=ceftriaxone and AST for strep. pneumonia: amoCl=R.*

When ceftriaxone is entered as PE (Fig. 7.5), the recalculated susceptibilities results in a new order of the recommended treatments. The *in vivo* coverage of ampicillin is affect by PE to ceftriaxone and consequently decreases from 61% (Fig. 7.4) to 58% (Fig. 7.6). The susceptibility to azithromycin is not affected, and hence azithromycin is now the top 1 recommendation instead of ampicillin. The decreased coverage of ceftriaxone itself results it in going from being the top 5 recommendation to drop down to be recommendation number 9 (see the red arrow).

When the AST result is entered that amoCl=R (Fig. 7.7), ampi is consequently not one of the recommended treatments (Fig. 7.8). Cross-resistance between amoCl and ampi results in a decreased probability of susceptibility to ampi, when resistance is observed towards amoCl.

As a part of the project, a feature to inspect the ABG was also implemented. Figure 7.9 shows an example of the implemented feature, in this case showing the susceptibility of *strep. pneumonia* to ceftriaxone. The susceptibility modification is illustrated on a bar representing susceptibility from 0 to 100%. The susceptibility from the ABG|CAI is indicated by a "●". Modifications made due to PE and/or AST results are indicated by a "◀". The green bar indicates the final susceptibility after in vivo modifications are made. In this example the susceptibility was not decreased by *in vivo* modifications.

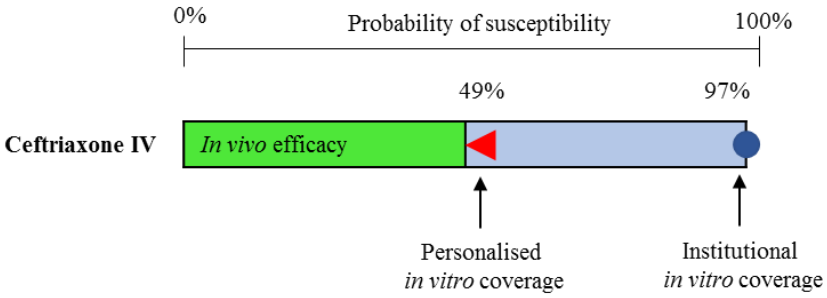


*Figure 7.9: An example of the implemented feature to inspect the probability of susceptibility. The example presents an ABG|CAI,PE,AST for the susceptibility of strep. pneumonia to ceftriaxone, when PE=ceftriaxone and AST: amoCl=R.*

Figure 7.10 shows additional versions of the ABG for the same patient. It can be seen that when PE=cftax is entered, then the susceptibility to cftax and ampi is decreased (ABG|CAI vs. ABG|CAI,PE). When an AST result is entered: amoCl=R, then the susceptibility to ampi and cftax is further decreased in the ABG|CAI,PE,AST.

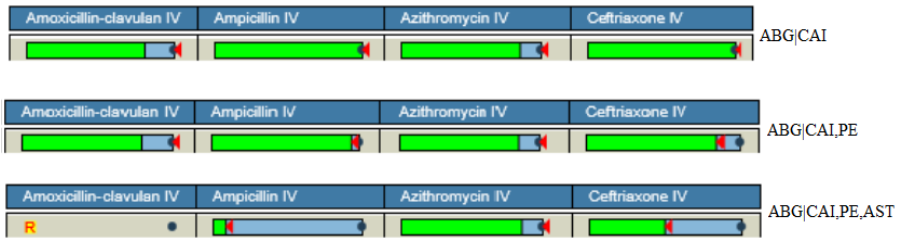


*Figure 7.10: Examples of the implemented personalised ABGs for a patient suspected of having a pneumonia infection.*

# CHAPTER 8. DISCUSSION

The aim of the project was to generate personalised ABGs for hospitalised infectious patients. We investigated how to modify an institutional ABG to account for three patient specific factors: Nosocomiality, prior exposure to antimicrobials, and AST results.

With regard to the nosocomiality of an infection, we found that when compared to CAIs, HAIs were associated with an increased probability of resistance by an OR of 1.94 (1.87-1.94). It is well known that the nosocomiality should be accounted for when selecting antimicrobial therapy (Doron and Davidson, 2011). Our results indicate that the effect of PE was even higher than the effect of nosocomiality for some antimicrobials. For example, for quinolones the OR for increased resistance was 3.35 (2.05-5.47) in GN bacteria isolated from patients exposed to any type of antimicrobials within the last month.

When AST results become available for a limited set of antimicrobials, the effect of cross-resistance and cross-susceptibility for all treatments available at a given hospital must be considered. We quantified the effect of cross-susceptibility/resistance between antimicrobials in a crossABG. We developed a method which modifies the susceptibility to the untested antimicrobials with respect to a patient's AST results, by using the crossABG. Our results indicate that ORs describing cross-susceptibility/resistance can be used to predict the susceptibility to untested antimicrobials.

We developed methods to combine the susceptibility modifications accounting for nosocomiality, PE, and AST, respectively. The methods were developed to be practical and easily implementable, and during the project we succeeded in implementing the methods in an existing software system for antimicrobial stewardship (TREAT).

Future work includes a validation of the method presented in Chapter 5, which was used to modify the ABG to prior exposure. The method presented in Chapter 6 should likewise be validated by making an attempt to recalculate the susceptibility, while including the effect of other AST results and PE.

In Chapter 2 we took steps to improve the quality of the susceptibilities presented in an institutional ABG. AST results from similar species were mapped into pathogen groups to decrease the risk of estimating susceptibilities on the basis of a few or zero results. The quality of the susceptibilities was further optimised by including AST results from a similar institution and by including opinions from experts. It should

also be considered whether the crossABG could likewise be improved, in cases of missing data, by using statistics from similar antimicrobials.

When quantifying the effect of prior antimicrobial exposure, we were not able to access data on exposure going further back than one month. The time since antimicrobial exposure is however a factor that affects the level of increased resistance, which may persist for up to 12 months (Costelloe et al., 2010). Studies reporting the quantity of antimicrobials prescribed found that longer duration and multiple courses were associated with higher rates of resistance (Costelloe et al., 2010). Hence the duration of prior antimicrobial treatment could also be considered as a patient specific factor.

Another patient specific factor, not addressed in the thesis, is clinically failing treatment. If a patient is not responding to a given antimicrobial treatment this could indicate that the pathogens causing the infection are resistant to the given treatment. In that case, the probability of susceptibility to the treatment should be adjusted and likewise for antimicrobials showing cross-resistance to the ineffective antimicrobial. Future studies could analyse data from patients with clinically failing treatment, to clarify how to generate personalised ABGs accounting for clinically failing treatment. These ABGs could be clinically important, when a current treatment fails and a new treatment should be selected.

The personalised ABGs generated in this project could serve as a better prediction of antimicrobial susceptibility than traditional institutional ABGs. Thereby the project seeks to contribute to patient specific antimicrobial stewardship by supporting clinicians in giving targeted personalised therapy and avoid failure of therapy due to resistant microbes.

# LITERATURE LIST

Andreassen, S., Zalounina, A., Leibovici, L., Paul, M., 2009. Learning susceptibility of a pathogen to antibiotics using data from similar pathogens. Methods Inf. Med. 48, 242–247.

Andreassen, S., Zalounina, A., Paul, M., Sanden, L., Leibovici, L., 2015. Interpretative reading of the antibiogram – a semi-naïve Bayesian approach. Artif. Intell. Med. 65, 209–217.

Bax, R., Bywater, R., Cornaglia, G., Goossens, H., Hunter, P., Isham, V., Jarlier, V., Jones, R., Phillips, I., Sahm, D., Senn, S., Struelens, M., Taylor, D., White, A., 2001. Surveillance of antimicrobial resistance — what, how and whither? Clin. Microbiol. Infect. 7, 316–325.

Baysari, M.T., Lehnbom, E.C., Li, L., Hargreaves, A., Day, R.O., Westbrook, J.I., 2016. The effectiveness of information technology to improve antimicrobial prescribing in hospitals: A systematic review and meta-analysis. Int. J. Med. Inform. 92, 15–34.

Bell, B.G., Schellevis, F., Stobberingh, E., Goossens, H., Pringle, M., 2014. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect. Dis. 14, 13.

Brier, G.W., 1950. Verification of forecasts expressed in terms of probability. Mon. Weather Rev. 78, 1–3.

CDC, 2016. Core Elements of Hospital Antibiotic Stewardship Programs [WWW Document]. Centers Dis. Control Prev. URL http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html (accessed 8.28.16).

Costelloe, C., Metcalfe, C., Lovering, A., Mant, D., Hay, A.D., 2010. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 340, c2096.

Courvalin, P., 1996. Interpretive reading of in vitro antibiotic susceptibility tests (the antibiogramme). Clin. Microbiol. Infect. 2, S26–S34.

Dellit, T.H., Owens, R.C., McGowan, J.E., Gerding, D.N., Weinstein, R.A., Burke, J.P., Huskins, C.W., Paterson, D.L., Fishman, N.O., Carpenter, C.F., Brennan, P.J., Billeter, M., Hooton, T.M., 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for

developing an institutional program to enhance antimicrobial stewardship. Clin. Infect. Dis. 44, 159–77.

Dellit, T.H., Owens, R.C., McGowan, J.E.J., Gerding, D.N., Weinstein, R.A., Burke, J.P., Huskins, W.C., Paterson, D.L., Fishman, N.O., Carpenter, C.F., Brennan, P.J., Billeter, M., Hooton, T.M., 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin. Infect. Dis. 44, 159–177.

Dickstein, Y., Geffen, Y., Leibovici, L., Paul, M., 2016. Comparison of Antibiotic Susceptibility Patterns of Bacterial Isolates Based on Time From Hospitalization and Culture Source: Implications for Hospital Antibiograms. Infect. Control Hosp. Epidemiol. 37.

Doron, S., Davidson, L.E., 2011. Antimicrobial stewardship. Mayo Clin. Proc. 86, 1113–23.

ECDC, 2015. Summary of the latest data on antibiotic consumption in the European Union [WWW Document]. Eur. Cent. Dis. Prev. Control. Stock. 2015. URL http://ecdc.europa.eu/en/eaad/antibiotics-news/Documents/antimicrobial-consumption-ESAC-Net-summary-2015.pdf (accessed 12.18.15).

ECDC, 2017. Antimicrobial Resistance and Healthcare-associated Infections Programme [WWW Document]. URL http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-resistance-healthcare-associated-infections-programme/Pages/ARHAI.aspx (accessed 3.12.17).

EUCAST, 2016. EUCAST Expert Rules Version 3.1 Intrinsic Resistance and Exceptional Phenotypes Tables.

Hindler, J.F., Stelling, J., 2007. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. Clin. Infect. Dis. 44, 867–73.

Kullar, R., Goff, D.A., Schulz, L.T., Fox, B.C., Rose, W.E., 2013. The “epic” challenge of optimizing antimicrobial stewardship: the role of electronic medical records and technology. Clin. Infect. Dis. 57, 1005–1013.

Leclercq, R., Cantón, R., Brown, D.F.J., Giske, C.G., Heisig, P., MacGowan, A.P., Mouton, J.W., Nordmann, P., Rodloff, A.C., Rossolini, G.M., Soussy, C.-J., Steinbakk, M., Winstanley, T.G., Kahlmeter, G., 2013. EUCAST expert rules in antimicrobial susceptibility testing. Clin. Microbiol. Infect. 19, 141–60.

Leibovici, L., Shraga, I., Andreassen, S., 1999. How do you choose antibiotic treatment? BMJ Br. Med. J. 318, 1614.

Leibovici, L., Shraga, I., Drucker, M., Konigsberger, H., Samra, Z., Pitlik, S.D., 1998. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J. Intern. Med. 244, 379–386.

MacDougall, C., Polk, R.E., 2005. Antimicrobial stewardship programs in health care systems. Clin. Microbiol. Rev. 18, 638–656.

Mandell, G.L., Bennett, J.E., Dolin, R., 2010. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th edition, 7th ed.

Pakyz, A.L., 2007. The utility of hospital antibiograms as tools for guiding empiric therapy and tracking resistance. Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy 27, 1306–12.

Paul, M., Andreassen, S., Tacconelli, E., Nielsen, A.D., Almanasreh, N., Frank, U., Cauda, R., Leibovici, L., 2006. Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial. J. Antimicrob. Chemother. 58, 1238–45.

Paul, M., Shani, V., Muchtar, E., Kariv, G., Robenshtok, E., Leibovici, L., 2010. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob. Agents Chemother. 54, 4851–4863.

Sanden, L., Hussein, H., Paul, M., Andreassen, S., 2017. Pathogen- and antimicrobial-specific resistance in late hospital-acquired infections. In: The 27th European Congress of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases.

Sanden, L., Paul, M., Leibovici, L., Andreassen, S., 2016. Quantifying the associations between antibiotic exposure and resistance - a step towards personalised antibiograms. Eur. J. Clin. Microbiol. Infect. Dis. 35, 1989–1996.

Schaechter, M., Engleberg, N.C., DiRita, V., Dermody, T.S., 2007. Schaechter's Mechanisms of Microbial Disease. Lippincott Williams & Wilkins.

Spiegelhalter, D.J., Dawid, A.P., Lauritzen, S.L., Cowell, R.G., 1993. Bayesian Analysis in Expert Systems. Stat. Sci. 8, 219–247.

TREATsystems.com, 2017. Antimicrobial Stewardship Program with TREAT Steward [WWW Document]. URL http://www.treatsystems.com/Default.aspx (accessed 2.3.17).

WHO, 2011. Race against time to develop new antibiotics. Bull. World Health Organ. 88, 88–89.

WHO, 2014. Antimicrobial Resistance: Global Report on Surveillance. Bull. World Health Organ. 61, 383–94.

# APPENDICES

# Appendix A.

# Modifying the resistance to an antimicrobial after PE to the same antimicrobial class

We assume that a given pathogen has an ABG presenting a set of N antimicrobials: N = {1, …, n, …, N} and a corresponding set of AST results: $\boldsymbol{A_N}$ = {$A_1$, …, $A_n$, …, $A_N$}, where $A_n$ is either susceptible ($a_n$) or resistant ($\neg a_n$).

The prior probability of susceptibility to an antimicrobial $A_n$, is denoted as $P(a_n)$. The corresponding probability of resistance to $A_n$ is denoted as $P(\neg a_n)$. Hence $P(\neg a_n) = 1 - P(a_n)$.

The aim is to calculate the posterior probability $P^*(\neg a_n)$ of resistance to antimicrobial $A_n$, given PE to an antimicrobial of the same class.

The idea was to use an OR for resistance, given PE to the same class of antimicrobials, denoted as $OR_{\neg a_n|PE=same}$.

First, we define the prior odds $OD_{\neg \boldsymbol{a_n}}$ for resistance to $A_n$ as:

$$OD_{\neg a_n} = P(\neg a_n)/P(a_n) \qquad \text{(Eq. 1)}$$

The posterior odds for resistance to $A_n$, given PE to the same class of antimicrobials is defined as:

$$OD^*_{\neg a_n} = P^*(\neg a_n)/P^*(a_n) \qquad \text{(Eq. 2)}$$

where $P(a_n)$ is the probability of resistance for patients without PE and $P^*(a_n)$ is the probability of resistance for patient with PE.

$OR_{\neg a_n|PE=same}$ is defined as:

$$OR_{\neg a_n|PE=same} = \frac{OD^*_{\neg a_n}}{OD_{\neg a_n}} = \frac{P^*(\neg a_n)}{P^*(a_n)} \cdot \frac{P(a_n)}{P(\neg a_n)} \qquad \text{(Eq. 3)}$$

By isolating $OD^*_{\neg a_n}$ in Eq. 3, we get:

$$OD^*_{\neg a_n} = OD_{\neg a_n} \cdot OR_{\neg a_{n|PE=same}} \quad \text{(Eq. 4)}$$

We assume that $P(a_n)$ is known from the patient's ABG and that $OR_{\neg a_n|PE=same}$ is known from Chapter 4. This allows calculation of $P(\neg a_n)$ = 1- $P(a_n)$, $OD_{\neg a_n}$ (Eq. 1), and $OD^*_{\neg a_n}$(Eq. 4), in that order.

Finally, the posterior probability of resistance, $P^*(\neg a_n)$, can then be calculated by using the mathematical relationship between odds and probability:

$$P^*(\neg a_n) = \frac{OD^*_{\neg a_n}}{1 + OD^*_{\neg a_n}} \quad \text{(Eq. 5)}$$

And if desired also $P^*(a_n)$ as:

$$P^*(a_n) = 1 - P^*(\neg a_n)$$

# Modifying the resistance to an antimicrobial after PE to other classes of antimicrobials

The question is now how to modify the probability of resistance to antimicrobials from other classes. Consider an antimicrobial $B$, which is a member of the set of $N$ antimicrobials and belongs to another class than the antimicrobial $A_n$, to which the patient was exposed. The prior probability of susceptibility to antimicrobial B, is denoted as $P(b)$. The corresponding probability of resistance to B is denoted as $P(\neg b)$. The aim is to calculate the posterior probability $P^*(\neg b)$ after exposure to $A_n$ has modified the probability of resistance to antimicrobial $A_n$ from $P(\neg a_n)$ to $P^*(\neg a_n)$.

Marginalisation of the joint probability of $P(B, A_n)$ gives:

$$P(\neg b) = P(\neg b, a_n) + P(\neg b, \neg a_n) \quad \text{(Eq. 6)}$$

By the first probability axiom we have:

$$P(\neg b) = P(\neg b|\, a_n) \cdot P(a_n) + P(\neg b|\neg a_n) \cdot P(\neg a_n) \quad \text{(Eq. 7)}$$

where $P(\neg b|A_n)$ is the vector of conditional probabilities of resistance to B given the outcome of $A_n$: $P(\neg b|a_n)$ and $P(\neg b|\neg a_n)$.

When we learn $P^*(a_n)$ (Eq. 5), our belief in B is revised, such that using Eq. 7 we have:

$$P^*(\neg b) = P(\neg b|\, a_n) \cdot P^*(a_n) + P(\neg b|\neg a_n) \cdot P^*(\neg a_n) \quad \text{(Eq. 8)}$$

where we assume that $P(\neg b|a_n)$ and $P(\neg b|\neg a_n)$ are available from a crossABG.

# The relation between ORs for susceptibility and ORs for resistance

The crossABG contains OR for susceptibility (Chapter 3), while the effect of PE is described as ORs for resistance (Chapter 5). This section explains how an OR for susceptibility mathematically be converted to an OR for resistance, which is convenient, when combining these.

$OR_{b|A_n}$ is the OR for *susceptibility* to an antimicrobial B (b), given the susceptibility to antimicrobial $A_n$ (susceptible ($a_n$) or resistant ($\neg a_n$)).

$OR_{\neg b|A_n}$ is the OR for *resistance* to antimicrobial B (¬b), due to PE to antimicrobial $A_n$.

$OR_{b|A_n}$ can be calculated from $OR_{\neg b|A_n}$ and visa versa, as demonstrated below:

$OR_{\neg b|A_n}$ is defined as:

$$OR_{\neg b|A_n} = \frac{OD_{\neg b|A_n}}{OD\neg_b} = \frac{P(\neg b|A_n)}{P(b|A_n)} \cdot \frac{P(b)}{P(\neg b)} \quad \text{(Eq. 9)}$$

and $OR_{b|A_n}$ is defined as:

$$OR_{b|A_n} = \frac{OD_{b|A_n}}{OD_b} = \frac{P(b|A_n)}{P(\neg b|A_n)} \cdot \frac{P(\neg b)}{P(b)} \quad \text{(Eq. 10)}$$

From Eq. 9 we have:

$$OR_{\neg b|A_n} \cdot \frac{P(b|A_n)}{P(\neg b|A_n)} \cdot \frac{P(\neg b)}{P(b)} = 1 \quad \text{(Eq. 11)}$$

which equals:

$$OR_{\neg b|A_n} \cdot \frac{OD_{b|A_n}}{OD_b} = 1 \quad \text{(Eq. 12)}$$

Using the definition of $OR_{b|A_n}$ from Eq. 10, we have:

$$OR_{\neg b|A_n} \cdot OR_{b|A_n} = 1 \quad \text{(Eq. 13)}$$

and hence:

$$OR_{b|A_n} = \frac{1}{OR_{\neg b|A_n}} \quad \text{(Eq. 14)}$$

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-935-9

AALBORG UNIVERSITY PRESS